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[1]Clinical Pharmacology Department, Fattouma Bourguiba Hospital Monastir, Tunisia, Monastir, Tunisia, [2]Laboratory LR12ES09 "Chemical, Galenic and Pharmacological Development of Drugs", Faculty of Pharmacy of Monastir, Tunisia, Monastir, Tunisia
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[1]Department of Clinical Pharmacology, St Olavs University Hospital, Trondheim, Norway, [2]Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway, [3]Department of Stroke, Clinic of Medicine, St. Olavs University Hospital,, Trondheim, Norway, [4]Clinic of Cardiology, St. Olavs University Hospital, Trondheim, Norway, [5]Department of Circulation and Medical Imaging, Norwegian University of Science and Technology , Trondheim, Norway, [6]Department of Clinical Chemistry, St. Olavs University Hospital, Trondheim, Norway, [7]Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway, [8]Regional Centre for Child and Youth Mental Health and Child Welfare, Department of mental Health, Faculty of medicine and health Sciences, Norwegian University of Science and Technology, Trondheim, Norway
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[1]Leiden University Medical Centrer, dept of Clinical Pharmacy and Toxicology, Leiden, the Netherlands, [2]Drug Analysis and Toxicology division of the Dutch Foundation for Quality Assessment in Medical Laboratories (SKML), Utrecht, the Netherlands, [3]Department of Hematologic Malignancies Translational Sciences and Department of Hematologic Malignancies & HCT, Beckman Research Institute at City of Hope, Duarte, USA, [4]Department of Clinical Pharmacy, Division of Laboratory Medicine and Pharmacy, University Medical Center Utrecht, Utrecht, the Netherlands, [5]Central Diagnostic Laboratory, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands, [6]Department of Clinical Pharmacology, University Medical Center Utrecht, Utrecht, the Netherlands, [7]Department of Clinical Pharmacy OLVG, Amsterdam, the Netherlands
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[1]The Second Xiangya Hospital of Central South University, Changsha, China
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[1]Mayo Clinic, Department of Laboratory Medicine & Pathology, Rochester, United States, [2]Mayo Clinic Health System, Department of Pharmacy, Eau Claire, United States, [3]Mayo Clinic, Department of Pharmacy, Rochester, United States, [4]Mayo Clinic, Division of Nephrology and Hypertension, Rochester, United States, [5]Mayo Clinic, Division of Public Health, Infectious Diseases and Occupational Medicine, Rochester, United States, [6]Mayo Clinic, Strategy Department, Rochester, United States

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[1]Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands, [2]Department of Clinical Pharmacology, Division Medical Oncology, The Netherlands Cancer institute, Amsterdam, The Netherlands, [3]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands, [4]Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands, [5]Department of Pharmacology, Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

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[1]Centre For Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway, [2]Department of Life Science and Health, OsloMet – Oslo Metropolitan University, Oslo, Norway, [3]Department of Physiology and Pharmacology, Section of Pharmacogenetics, Karolinska Institutet, Stockholm, Sweden, [4]Department of Pharmacy, University of Oslo, Oslo, Norway

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[1]Department of Laboratory Medicine, Diagnostic Clinic, University Hospital of North Norway, Tromsø, Norway

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[1]Pharmacology Research Unit, Research Center CHU Sainte-Justine, Montreal, Canada, [2]Division of Pediatric Hematology/Oncology, Department of Pediatrics, Charles-Bruneau Cancer Center, CHU Sainte-Justine, Montreal, Canada, [3]Clinical Pharmacology Laboratory, OPTILAB CHU Sainte-Justine, Montreal, Canada

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[1]Beijing Diagreat Biotechnologies Co., Ltd, , China

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[1]Medical Unit of Clinical Pharmacology, Medical Diagnostics Karolinska, Karolinska University Hospital, , Sweden

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[1]Medical Unit of Clinical Pharmacology, Medical Diagnostics Karolinska, Karolinska University Hospital, Stockholm, Sweden, [2]Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden

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[1]Depaetment Of Pathology, Faculty Of Medicine, Mahidol University, Bangkok, Thailand, [2]Laboratoire de Pharmacologie, Institut Claudius-Regaud, Institut Universitaire du Cancer de Toulouse Oncopole, Centre de Recherche en Cancérologie de Toulouse, INSERM U1037, Université Paul Sabatier,, Toulouse, France, [3]Division of Hematology-Oncology, Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

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[1]Thammasat University, Pathum Thani, Thailand, [2]Department of Clinical Chemistry, Faculty of Allied Health Sciences, Chulalongkorn University, , Thailand, [3]Division of Medical Oncology, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, , Thailand, [4]Department of Pathology, Faculty of Medicine, Srinakharinwirot University, Nakhonnayok, , Thailand, [5]Division of Pharmacogenomics and Personalized Medicine, Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, , Thailand, [6]Division of General Pharmacy Practice,

Department of Pharmaceutical Care, College of Pharmacy, Rangsit University, , Thailand, [7]Cancer Research Center of Toulouse, INSERM, UMR-1037, CNRS ERL5294, Paul Sabatier University, , France

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[1]Agency for Medicinal Product and Medical Devices of Croatia, , Croatia, [2]Division of Pharmacy and Optometry, University of Manchester, Manchester, United Kingdom , [3]Division of Pharmacogenomics and Therapy Individualization, Department of Laboratory Diagnostics, University Hospital Centre Zagreb, Zagreb, Croatia , [4]Department of Psychiatry, University Hospital Centre Zagreb, Zagreb, Croatia, [5]Analytical Toxicology and Pharmacology Division, Department of Laboratory Diagnostics, University Hospital Centre Zagreb, Zagreb, Croatia, [6]Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia

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[1]Theradiag, Croissy Beaubourg, France

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[1]Inserm U1248 University Of Limoges, Limoges, France, [2]Limoges University Hospital, Limoges, France

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[1]University of California, Santa Barbara, Santa Barbara, United States, [2]Monash University, Parkville, Australia

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[1]Second Xiangya Hospital, Central South University, Changsha, China

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[1]China-Japan Friendship Hospital, 2 Yinghuadongjie Street, Chaoyang, Beijing, China

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[1]Department of Clinical Pharmacy, the Second Xiangya Hospital of Central South University, Changsha, China, [2]Institute of Clinical Pharmacy, Central South University, Changsha, China, [3]School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing, China, [4]Department of Infectious Disease, the Second Xiangya Hospital of Central South University,

Changsha, China, [5]School of Medicine, University of Sydney, Sydney, Australia, [6]Centre for Infectious Diseases and Microbiology, Westmead Hospital, Sydney, Australia

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[1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea, [2]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea, [3]Department of Laboratory Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea, [4]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [5]Department of Infectious disease, Ajou University School of Medicine, Suwon, Republic of Korea

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[1]Christian Medical College, Vellore, Vellore, India, [2]Keck School of Medicine, , United States of America

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[1]SCIEX, , United Kingdom, [2]SCIEX, , USA

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[1]CHC Rijeka, Rijeka, Croatia

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[1]Centre de Biologie Sud - LBMMS, Lyon, France

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[1]Department of Pharmacy, National Cancer Center Hospital, Tokyo, Japan, [2]Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan, [3]Department of Medical Oncology, National Cancer Center Hospital, Tokyo, Japan, [4]Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan, [5]Department of Head and Neck, Esophageal Medical Oncology / Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan, [6]Translational Research Specimen Control Section, National Cancer Center Hospital, Tokyo, Japan, [7]SHIMADZU CORPORATION, Kyoto, Japan

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Ms Maria Swartling[1], Anna-Karin Hamberg[2], Mia Furebring[3], Thomas Tängdén[3], Elisabet I Nielsen[1]

[1]Department of Pharmacy, Uppsala University, Uppsala, Sweden, [2]Department of Clinical Chemistry and Pharmacology, Uppsala University Hospital, Uppsala, Sweden, [3]Department of Medical Sciences, Infection Medicine, Uppsala University, Uppsala, Sweden

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Georges Khater[1], CEO Simon Davière[1], R&D Director Guillaume Nogier[1], Project Manager Amandine Puig[1], Project Manager Christophe Montaillier[1]

[1]Theradiag, Croissy Beaubourg, France

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[1]SCIEX, , United Kingdom

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[1]Laboratory of Toxicology, Ghent University, Ghent, Belgium, [2]Laboratory of Clinical Chemistry and Hematology, Ghent University Hospital, Ghent, Belgium, [3]CAMAG, Muttenz, Switzerland

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[1]Liver and Digestive Diseases Networking Biomedical Research Centre (CIBERehd), Pharmacology and Toxicology, Biomedical Diagnostic Center (CDB), Hospital Clínic Barcelona, IDIBAPS, University of Barcelona, Barcelona, Spain, , Spain, [2]Liver Transplant Unit, Hospital Clinic Barcelona, IDIBAPS, CIBERehd, University of Barcelona, Barcelona, Spain, , Spain, [3]Biochemistry and Molecular Genetics, Biomedical Diagnostic Center, Hospital Clínic Barcelona, Barcelona, Spain, , Spain, [4]Department of General and Digestive Surgery, Hospital Clínic Barcelona, IDIBAPS, CIBERehd, University of Barcelona, Barcelona, Spain, , , [5]Pharmacology and Toxicology, Biomedical Diagnostic Center (CDB), Hospital Clínic Barcelona, IDIBAPS, CIBERehd, University of Barcelona, Barcelona, Spain, ,

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[1]Department of Pharmacy, National Cerebral and Cardiovascular Center, Osaka, Japan, [2]Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, USA, [3]Department of Pediatric Cardiovascular Surgery, National Cerebral and Cardiovascular Center, Osaka, Japan, [4] Department of Pediatric Cardiology, National Cerebral and Cardiovascular Center, Osaka, Japan, [5]Department of Hospital Pharmacy, Graduate School of Medicine, Osaka University, Osaka, Japan

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MSc MPharm Arkadiusz Kocur[1,2], PhD MD Jacek Rubik[3], MSc Agnieszka Czajkowska[2], PhD PharmD Tomasz Pawiński[1]

[1]Medical University of Warsaw Department of Drug Chemistry, Warsaw, Poland, [2]Department of Biochemistry, Radioimmunology, and Experimental Medicine, Pharmacokinetics Laboratory, The Children's Memorial Health Institute, Warsaw , Poland, [3]Department of Nephrology, Kidney Transplantation, and Arterial Hypertension, The Children's Memorial Health Institute, Warsaw , Poland

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Dr. Nan Hu[1], Mrs Liying Wang[1], Mr Rong Chen[1]

[1]The Third Affiliated Hospital of Soochow University, Changzhou, China

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[1]Pharmacology and Toxicology Laboratory, Biochemistry and Molecular Genetics Department, Biomedical Diagnostic Center, Hospital Clinic of Barcelona, Barcelona, Spain, [2]Liver Unit, Hospital Clinic Barcelona, IDIBAPS, CIBEREHD, Barcelona, Spain, [3]Pharmacology and Toxicology Laboratory, Biochemistry and Molecular Genetics Department, Biomedical Diagnostic Center, Hospital Clinic of Barcelona, University of Barcelona, IDIBAPS, CIBERehd, Barcelona, Spain

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[1]Chromatography and Mass Spectrometry Section, Central Laboratory of Analysis, IRCCS Istituto Giannina Gaslini, Genoa, Italy, [2]Department of Internal Medicine, Pharmacology & Toxicology Unit, University of Genoa, Genoa, Italy, [3]Clinical Pharmacology Unit, EO Ospedali Galliera, Genoa, Italy, [4]UOC Reumatologia e Malattie Autoinfiammatorie , IRCCS Istituto Giannina Gaslini, Genoa, Italy

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[1]Ghent University Hospital, Ghent, Belgium, [2]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium

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Laure Ponthier[1,2], PharmD/PhD Benedicte Franck[3], MD/PhD Julie Autmizguine[4,5], PharmD/PhD Jean Baptiste Woillard[2]

[1]Pediatric intensive care unit, Limoges, France, [2]INSERM U 1248 Pharmacology and Transplantation, Limoges, France , [3]Pharmacology, Rennes, France, [4]Department of Pediatrics, Montreal , Quebec, Canada, [5]Department of Pharmacology and Physiology, Montreal, Quebec,Canada

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PharmD Tomasz Pawiński[1], MSc Arkadiusz Kocur[1,2], Dr Jacek Rubik[3], MSc Agnieszka Czajkowska[2]

[1]Department of Drug Chemistry, Medical University of Warsaw, Warsaw, Poland, [2]Department of Biochemistry, Radioimmunology, and Experimental Medicine, Pharmacokinetics Laboratory, The Children`s Memorial Health Institute, Warsaw, Poland, [3]Department of Nephrology, Kidney Transplantation, and Arterial Hypertension, The Children`s Memorial Health Institute, Warsaw, Poland

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Dr Van Dong Nguyen[1,2], Ms Alice Côté[1], Dr Amélie Marsot[1]

[1]Faculty of Pharmacy of University Of Montreal, Montreal, Canada, [2]Department of Pharmacy of McGill University Healthcare Center, Montreal, Canada

69 TDM of tyrosine kinase inhibitors via VAMS collection at home

Dr Nick Verougstraete[1,2], Prof Christophe Stove[2]
[1]Department of Laboratory Medicine, Ghent University Hospital, Gent, Belgium, [2]Laboratory of Toxicology, Ghent University, Gent, Belgium

70 Quantification of rifampicin in a small volume of human plasma by UPLC-MS/MS with addressing the carryover issue

Takuya Sano[1], Takuho Ishii[1], Koichiro Hotta[2], Dr. Yuji Mano[2,3]
[1]Sunplanet Co., Ltd., Tsukuba, Japan, [2]Eisai Co., Ltd., Tsukuba, Japan, [3]University of Tsukuba, Tsukuba, Japan

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Dr Rekha Pai Mangalore[1,2], Mr Jeff Shao[1,2], Ms Lucy Tang[1,2], Ms Qiaoran Tu[1,2], Dr Amin Hajamohideen[3], Dr Simran Bhopal[4], Prof Trisha Peel[1,2], Prof Andrew Udy[1,2], A/Prof Denis Spelman[1,2], Prof Anton Peleg[1,2]
[1]Alfred Health, Melbourne, Australia, [2]Monash University, Melbourne, Australia, [3]St Vincent's Hospital, Melbourne, Australia, [4]Royal Children's Hospital, Melbourne, Australia

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Dr. Kazutaka Oda[1], Ms. Ayami Yamaguchi, Mr. Naoya Matsumoto, Dr. Hirotomo Nakata, Dr. Yusuke Highchi, Dr. Kisato Nosaka, Dr. Hirofumi Jono, Dr. Hideyuki Saito
[1]Kumamoto University Hospital, Kumamoto, Japan

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Ms Thi Nguyen[1], Dr Ranita Kirubakaran[2,3,4], Dr Hayley Schultz[5], Ms Sherilyn Wong[5], A/Prof Stephanie Reuter[5], Dr Brendan McMullan[6,7], Srinivas Bolisetty[7], Craig Campbell[8], Andrea Horvath[8], Dr Sophie Stocker[1,2,3]
[1]School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, Camperdown, Australia, [2]School of Clinical Medicine, Faculty of Medicine and Health, University of New South Wales, Kensington, Australia, [3]Department of Clinical Pharmacology and Toxicology, St. Vincent's Hospital, Darlinghurst, Australia, [4]Seberang Jaya Hospital, , Malaysia, [5]Clinical & Health Sciences, University of South Australia, Adelaide, Australia, [6]Department of Immunology and Infectious Diseases, Sydney Children's Hospital, Randwick, Australia, [7]Faculty of Medicine and Health, University of New South Wales, Kensington, Australia, [8]NSW Health Pathology, Department of Chemical Pathology, Prince of Wales Hospital, Sydney, Australia

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Bsc Soma Bahmany[1], MSc Moska Hassanzai[1], Dr Robert Flint[1], Dr Hein van Onzenoort[2], Dr Brenda C.M. de Winter[1], Prof. Dr. Birgit C.P. Koch[1]
[1]Erasmus Medical Center, Rotterdam, Netherlands, [2]Radboud Medical Center, Nijmegen, Netherlands

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Dr Rekha Pai Mangalore[1], Prof Trisha Peel[1], Prof Andrew Udy[1], Prof Anton Peleg[1], Dr Darshini Ayton[2]
[1]Alfred Health/Monash University, Melbourne, Australia, [2]Monash University, Melbourne, Australia

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Kohei Yoshikawa[1], Toshikazu Minohata[1]
[1]Shimadzu Corporation, Kyoto, Japan

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[1]Department of Pharmacy, Kobe University Hospital, Kobe, Japan, [2]Division of Urology, Kobe University Graduate School of Medicine, Kobe, Japan
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[1]Institute for Clinical Chemistry / Interdisciplinary UMG Laboratories, University Medical Center Goettingen, Göttingen, Germany, [2]Department of Nephrology and Rheumatology, University Medical Center Goettingen, Göttingen, Germany, [3]Department of Anesthesiology, University Medical Center Goettingen, Göttingen, Deutschland
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[1]Department of Clinical Pharmacology, Division of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands, [2]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands, [3]Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands, [4]Department of Medical Oncology, Radboud University Medical Center, Nijmegen, The Netherlands, [5]Department of Pharmacology, Radboud University Medical Center, Nijmegen, The Netherlands, [6]Department of Medical Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [7]Department of Pharmacy, Erasmus Medical Center, Rotterdam, The Netherlands, [8]Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, The Netherlands, [9]Department of Medical Oncology, Deventer Hospital, Deventer, The Netherlands, [10]Department of Medical Oncology, Reinier de Graaf Hospital, Delft, The Netherlands, [11]Department of Medical Oncology, Meander Medical Center, Amersfoort, The Netherlands, [12]Department of Medical Oncology, Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands, [13]Department of Medical Oncology, St. Antonius Hospital, Nieuwegein, Nieuwegein, The Netherlands, [14]Department of Medical Oncology, Isala Clinics, Zwolle, The Netherlands, [15]Department of Medical Oncology, Franciscus Gasthuis & Vlietland, Schiedam, The Netherlands, [16]Department of Pharmacy, Gelderse Vallei Hospital, Ede, The Netherlands, [17]Department of Medical Oncology, Haaglanden Medical Center, The Hague, The Netherlands, [18]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [19]Department of Medical Oncology, Leiden University Medical Center, Leiden, The Netherlands, [20]Department of Clinical Pharmacy, Utrecht University Medical Center, Utrecht, The Netherlands, [21]Department of Pharmacology, Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands
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[1]Institute For Clinical Chemistry / Interdisciplinary Umg Laboratories University Medical Center Göttingen Germany, Goettingen , Germany, [2]Department of General-, Visceral- and Pediatric surgery, University Medical Center Goettingen, Goettingen, Germany
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[1]Erasmus MC Dept. of Hospital Pharmacy, Rotterdam, Netherlands, [2]Erasmus MC Dept. of Medical Oncology, Rotterdam, Netherlands, [3]Erasmus MC Rotterdam Clinical Pharmacometrics Group, Rotterdam, Netherlands

88 Saliva-based assay to measure the concentration of pyrazinamide using a mobile UV Spectrophotometer

Mr Ricky Hao Chen[1,2], Ms Thi Nguyen[1,2], Dr Hannah Yejin Kim[1,3,4], Dr Sophie L. Stocker[1,5,6], Johannes Alffenaar[1,2,3]

[1]Sydney Pharmacy School, Faculty of Medicine and Health, The University of Sydney, Camperdown, Australia, [2]Westmead Hospital, Westmead, Australia, [3]Sydney Institute for Infectious Diseases, University of Sydney, Sydney, Australia, [4]Department of Pharmacy, Westmead Hospital, Westmead, Australia, [5]Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Darlinghurst, Australia, [6]St Vincent's Clinical Campus, School of Clinical Medicine, The University of New South Wales, Darlinghurst, Australia

89 A quantitative method for the analysis of ivacaftor, hydroxymethyl ivacaftor, ivacaftor carboxylate, tezacaftor, M1-tezacaftor, elexacaftor and M23-elexacaftor in plasma and dried blood spots using LC-MS/MS

Mrs Marloes Vos- Van Der Meer[1], PharmD Steffie E.M. Vonk[1], Dennis T.D. van der Laan[1], PharmD, PhD Yuma A. Bijleveld[1], Renate Kos[2], PhD Anke H. Maitland[2], PhD Marleen E. Kemper[1], PharmD, PhD Ron A.A. Mathôt[1]

[1]Amsterdam UMC location University of Amsterdam, Department of Pharmacy & Clinical Pharmacology, Amsterdam, The Netherlands, [2]Amsterdam UMC location University of Amsterdam, Department of Pulmonary Medicine, Amsterdam, The Netherlands

90 Towards precision dosing in psychiatry: population pharmacokinetics meta modelling of clozapine and lithium.

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[1]Aix-marseille Université, , France, [2]Exactcure, , France, [3]Service de Pharmacologie clinique et Pharmacovigilance, Hôpital de la Timone, , France, [4]Aix-Marseille Univ, AP-HM, CNRS, INT, Inst Neurosci Timone, Hôpital Sainte Marguerite, Pôle de psychiatrie, , France, [5]Département de psychiatrie, Sainte Marguerite University Hospital, Assistance Publique- Hôpitaux de Marseille, , France

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Dr Sarah Alghanem[1]

[1]College of Pharmacy at Kuwait University, , Kuwait

92 Ixekizumab Trough Concentrations in Psoriasis: Paving the Way towards Personalized Therapy - A Cohort Study

dr. Lisa Schots[1], dr. Rani Soenen[1], dr. Debby Thomas[2], dr. Erwin Dreesen[2], Prof. dr. Jo Lambert[1]

[1]Department of Dermatology, Ghent University Hospital, Ghent, Belgium, [2]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium, [3]3. Department of Dermatology, AZ Delta, Torhout, Belgium

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MSc Robin Weijland[1,3], PhD Naomi Van der Linden[2], Professor Ruud Verdaasdonk[3], PhD, PharmD Dina Kweekel[1]

[1]Leiden University Medical Center, Leiden, the Netherlands, [2]TU Delft, Institute for Health Systems Science, Delft, the Netherlands, [3]University of Twente, TechMed Center, Enschede, the Netherlands

95 Population pharmacokinetics of lenalidomide in Chinese patients with B-cell malignancies

Dr. Yi Ma[1], Mr. Zaiwei Song[1], Mr. Hao Bing[1,2], Mr. Huan He[2], Prof. Libo Zhao[1], Prof. Rongsheng Zhao[1]

[1]Peking University Third Hospital, , China, [2]Beijing Children's Hospital, , China

96 Quantification of four CFTR-modulators in plasma and breastmilk by LC-HRMS

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[1]Medical Unit for Clinical Pharmacology, Karolinska University Hospital, Stockholm, Sweden, [2]Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Institute, Stockholm, Sweden, [3]Clinical Epidemiology Division, Karolinska Institutet, Stockholm, Sweden
97 Development and validation of an LC-MS/MS method for quantification of total and unbound concentration of vancomycin
PhD Jennie Östervall[1,2], MD, PhD Erik Eliasson[1,2], PhD Victoria Barclay[1,2]
[1]Medical Unit for Clinical Pharmacology, Karolinska University Hospital, Stockholm, Sweden, [2]Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Institute, Stockholm, Sweden
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[1]Peking University Third Hospital, , China
99 Validation of a LC-MS/MS method for quantification of Ampicillin in plasma
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[1]Sahlgrenska University Hospital, , Sweden
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[1]Maasstad Ziekenhuis, , Netherlands
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[1]Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, Netherlands, [2]Department of Obstetrics and Gynaecology, Rotterdam, Netherlands, [3]Department of Pediatrics, Division of Neonatology, Rotterdam, Netherlands, [4]Department of Internal Medicine, Division of Endocrinology, Erasmus University Medical Center, Rotterdam, Netherlands, [5]Department of Clinical Chemistry, Erasmus University Medical Center, Rotterdam, Netherlands, [6]Center for Antimicrobial Treatment Optimization Rotterdam (CATOR), , Netherlands, [7]Rotterdam Clinical Pharmacometrics Group, the Netherlands, , Netherlands, [8]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium, [9]Department of Development and Regeneration, KU Leuven, Leuven, Belgium, [10]Leuven Child and Youth Institute, KU Leuven, , Belgium
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[1]Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail)-UMR_S 1085, Rennes, France
103 How antiretroviral therapy could be affected by physical activity, oxidative stress and genetics: a multidisciplinary pilot study in people with HIV.
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[1]University of Turin, Department of Medical Sciences, TURIN, Italy, [2]Department of Medical Sciences, NeuroMuscolarFunction | Research Group, University of Turin, TURIN, ITALY, [3]ASL Città di Torino, Amedeo di Savoia Hospital, TURIN, ITALY, [4] Unit of Infectious Diseases, Department of Medical Sciences, University of Turin, Amedeo di Savoia Hospital, TURIN, ITALY, [5]Laboratory of Clinical

Pharmacology S.Luigi A.O.U., Department of Clinical and Biological Sciences, University of Turin, REGIONE GONZOLE, ORBASSANO, ITALY

104 Clozapine plasma concentrations in schizofrenic patients: a possible role of vitamin D related gene variants

Dr Alessandra Manca[1], Dr Alice Palermiti[1], Dr Jacopo Mula[1], Dr Miriam Antonucci[2], Dr Domenico Maiese[1], Dr Gianluca Bianco[1], Dr Elisa Delia De Vivo[1], Dr Flavio Vischia[3], Dr David De Cori[3], Dr Sara Venturello[4], Dr Guido Emanuelli[5], Prof Jessica Cusato[1], Prof Antonio D'Avolio[1]

[1]Laboratory of Clinical Pharmacology and Pharmacogenetics; Department of Medical Sciences, University of Turin, Amedeo di Savoia Hospital, Turin, Italy. , , , [2]SCDU Infectious Diseases, Amedeo di Savoia Hospital, ASL Città di Torino, 10149 Italy., , , [3]Department of Mental Health – Psychiatric Unit West Turin , Italy., , , [4]Department of Mental Health–Psychiatric Unit East, Day Service S.G. Bosco 10144-Turin, Italy., , , [5]Department of Mental Health–Psychiatric Unit East, S.G. Bosco 10144-Turin, Italy., ,

105 Fluconazole resistant urinary candidiasis: Can voriconazole be used as an alternative treatment?

Dr Christelle Boglione-Kerrien[1], Pr Jean-Pierre Gangneux[1], Dr Elodie Gautier-Veyret[2], Dr Thibaut Gelé[3], Dr Anne Hulin[3], Dr Sarah Baklouti[4], Dr Françoise Botterel[3], Dr Bénédicte Franck[1], Dr Sébastien Lalanne[1], Dr Camille Tron[1], Dr Fabrice Taïeb[1], Dr Marie-Clémence Verdier[1], Pr Eric Bellissant[1], Dr Florian Lemaitre[1]

[1]Rennes University Hospital, Rennes, France, [2]Grenoble Alpes Univeristy Hospital, Grenoble, France, [3]Henri Mondor University Hospital, Créteil, France, [4]IFB, Hôpital Purpan, Toulouse, France

107 QUANTIFYING THE EFFECT OF METHOTREXATE ON THE ADALIMUMAB RESPONSE IN PSORIASIS BY PHARMACOKINETIC-PHARMACODYNAMIC MODELLING

MD A.M. van Huizen[1], Paul Bank[2,3,4], MD, PhD1 G.E. van der Kraaij[1], MD A.H. Musters[1], MD, PhD C.I. Busard[1], MD, PhD S.P. Menting,[5], PhD T. Rispens,[6], PhD A. de Vries[7], MD, PhD M.B.A. van Doorn[8,9], MD, PhD E. Prens[8], MD, PhD J. Lambert[10], MD, PhD J.M.P.A. van den Reek[11], MD, PhD E.M.G.J. de Jong, PharmD, PhD R.A.A Mathôt, PharmD,[2], MD, PhD P.I. Spuls[1]

[1]Amsterdam UMC, Department of Dermatology, Amsterdam, The Netherlands, [2]Department of Hospital Pharmacy & Clinical Pharmacology, Amsterdam, The Netherlands, [3]NorthWest Clinics, Alkmaar, Netherlands, [4]Red Cross Hospital, Department of Hospital Pharmacy, Beverwijk, The Netherlands, [5]OLVG, Department of Dermatology, Amsterdam, The Netherlands, [6]Sanquin Research and Landsteiner Laboratory Academic Medical Center, Department of Blood Cell Research, Amsterdam, The Netherlands, [7]Sanquin Diagnostic Services, Amsterdam, The Netherlands, [8]Erasmus MC, Department of Dermatology, Rotterdam, The Netherlands, [9]Centre for Human Drug Research, Leiden, The Netherlands, [10]Ghent University Hospital, Department of Dermatology, Ghent, Belgium, [11]Radboud UMC, Department of Dermatology, Nijmegen, The Netherlands

110 Predicting the Pharmacokinetics of Voriconazole in Patients with Cirrhosis and Supporting CYP2C19 Phenotype-Guided Dose Optimization by Physiologically Based Pharmacokinetic Modeling

Doctor Taotao Wang[1], Miss Jiaojiao Chen, Miss Sihan Li

[1]The First Affiliated Hospital Of Xi'an Jiaotong University, , China

111 Real-time inhalants particle emission monitoring for non-invasive prediction of lung deposition

Dr Daiki Hira[1], Ms Sakiko Hatazoe[2], Dr Tetsuri Kondo[3], Dr Satoshi Ueshima[2], Dr Tomonobu Okano[2], Dr Mikio Kakumoto[2], Dr Tomohiro Terada[1]

[1]Department of Clinical Pharmacology and Therapeutics, Kyoto University Hospital, Kyoto, Japan, [2]College of Pharmaceutical Sciences, Ritsumeikan University, Kusatsu, Japan, [3]Department of Respiratory Medicine, Shonan Fujisawa Tokushukai Hospital, Fujisawa, Japan

113 Coadministration of voriconazole and rifabutin may increase the risk of adverse drug reactions in patients with multiple infections

MD Yoonjin Kim[1], MD Sungyeun Bae[1], MD, Ph.D Youngran Yoon[2], MD, Ph.D Jaeseong Oh[1], MD, Ph.D Injin Jang[1]

[1]Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea, [2]Kyungpook National University School of Medicine, Daegu, Republic of Korea

115 24/7 fully automated therapeutic drug analysis by LC/MS/MS

Mrs Aurore Jaffuel[1], Dr. Frank Streit[2], Prof. Dr. Andreas Fischer[2], Kohei Yoshikawa

[1]Shimadzu Corporation Japan, Kyoto, Japan, [2]Department of Clinical Chemistry, University Medical Center Goettingen, Goettingen, Germany

118 Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19

Ryo Tamura[1], Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19 Kei Irie[2,5], Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19 Atsushi Nakagawa[3], Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19 Hirohito Muroi[1], Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19 Masaaki Eto[4], Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19 Hiroaki Ikesue[1], Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19 Nobuyuki Muroi[1,5], Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19 Shoji Fukushima[2], Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19 Keisuke Tomii[3], Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19 Tohru Hashida[2,5]

[1]Department of Pharmacy, Kobe City Medical Center General Hospital, Kobe, Japan, [2]Faculty of Pharmaceutical Science, Kobe Gakuin University, Kobe, Japan, [3]Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan, [4]Department of Clinical Laboratory, Kobe City Medical Center General Hospital, Kobe, Japan, [5]Department of Clinical Pharmacy Research, Center for Clinical Research and Innovation, Kobe City Medical Center General Hospital, Kobe, Japan

120 Capillary application of (volumetric) dried blood spot assays for tacrolimus and creatinine determination in stem cell transplant patients.

Pharmd Hanna De Baets[1]

[1]Ghent University, Ghent, Belgium

121 Pharmacokinetic variability and markers of toxicity of valproate in patients with refractory epilepsy

Martha Wolden[2], Johan Sætre[2], Katrine Heger[2], MD, PhD Erik Sætre[4], MD, PhD Margrete L Burns[3], MSc Signe F Kjeldsen[3], PhD Svein I Johannessen[3,4], Professor Cecilie Johannessen Landmark[1]

[1]Oslo Metropolitan University And National Center For Epilepsy And Dept Of Pharmacology, Oslo University Hospital, Oslo, Norway, [2]Oslo Metropolitan Unversity, Dept of Pharmacy, Oslo, Norway, [3]Section for Clinical Pharmacology, Dept of Pharmacology, Oslo University Hospital, Oslo, Norway, [4]National center for epilepsy, Oslo University hospital, Oslo, Norway

122 Near-infrared-based hematocrit prediction using volumetric absorptive microsampling devices: an in-depth evaluation

Laura Boffel[1], Pharm. D. Liesl Heughebaert[1], Dr. Stijn Lambrecht[2], Dr. Christoph Lühr[3], Prof. Dr. Christophe Stove[1]

[1]Ghent University, Ghent, Belgium, [2]Ghent University Hospital, Ghent, Belgium, [3]BÜCHI Labortechnik GmbH, Essen, Germany

124 Modelling changes in the pharmacokinetics of tacrolimus during pregnancy after kidney transplantation: a retrospective cohort study

Drs. Maaike Schagen[1,2], PharmD Asiye Nur Ulu[2], Bsc Marith Francke[1,2], Prof. dr. Ron van Schaik[3], Dr. Jacqueline van de Wetering[1], Dr. Marleen van Buren[1], Dr. Dennis Hesselink[1], PharmD, PhD Brenda de Winter[2]

[1]Erasmus Medical Center Transplant Institute, Department of Internal Medicine, University Medical Center Rotterdam, Rotterdam, Netherlands, [2]Rotterdam Clinical Pharmacometrics Group, Department of Hospital Pharmacy, University Medical Center Rotterdam, Rotterdam, Netherlands, [3]Department of Clinical Chemistry, University Medical Center Rotterdam, , Rotterdam, Netherlands

126 Significance of CYP3A5 Polymorphism Analysis in the Prophylaxis of Graft-versus-Host Disease with Tacrolimus

Dr. Naoki Yoshikawa[1], Prof. Ryuji Ikeda[1]
[1]Department of Pharmacy, University of Miyazaki Hospital, Miyazaki, Japan

127 Adalimumab through levels as a predictor of patient-reported outcomes and disease activity in rheumatoid arthritis

PharmD Juul Cox[1,2,3], Dr. PharmD Tessa Bosch[1,2], Prof. dr. Angelique Weel[3,4]
[1]Hospital Pharmacy, Maasstad Hospital, Rotterdam, Netherlands, [2]Clinical Pharmacology and Toxicology, MaasstadLab Maasstad Hospital, Rotterdam, Netherlands, [3]Erasmus School of Health Policy & Management, Erasmus University Rotterdam, Rotterdam, Netherlands, [4]Rheumatology, Maasstad Hospital, Rotterdam, Netherlands

128 Implementation of finger prick blood sampling to support TDM of biologics: biologics concentration combined with an inflammatory marker

Phd Maurice Steenhuis[1], PhD Annick de Vries[1], PhD Theo Rispens[6], Tim Otten[2], Marijn Visschedijk[2], Arno Bourgonje, Alyssa Toorop[3], Zoé van Kempen, Laura Boekel, Yaëlle Besten[4], Joep Killestein[3], Gertjan Wolbink[4], Sander Tas[5], PhD Floris Loeff[1], Annick de Vries[1]
[1]Sanquin Diagnostic Services, Amsterdam, Netherlands, [2]Department of Gastroenterology, University Medical Centre Groningen, Groningen, The Netherlands, , , [3]Neurology Outpatient Clinic, Amsterdam UMC location Vrije Universiteit Amsterdam, Amsterdam, The Netherlands., , , [4]Amsterdam Rheumatology and Immunology Center, location Reade, Department of Rheumatology, Amsterdam, Netherlands., , , [5]Department of Rheumatology and Clinical, Amsterdam UMC, location AMC, University of Amsterdam, Amsterdam, the Netherlands., , , [6]Department of immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, Amsterdam, the Netherlands., ,

130 Pharmacokinetic variability of cannabidiol and its metabolites in patients with refractory epilepsy

Johan Sætre[2], Martha Wolden[2], PhD André Gottås[3], MSc Tao McQuade[4], MSc Signe F Kjeldsen[3], MD Anne Våtevik[5], MD, PhD Erik Sætre[5], MD, PhD Torleiv Svendsen[5,6], MD, PhD Margrete L Burns[3], PhD Svein I Johannessen[3,5], PhD Elisabeth L Øiestad[4], Professor Cecilie Johannessen Landmark[1]
[1]Oslo Metropolitan University and National Center For Epilepsy And Dept Of Pharmacology, Oslo University Hospital, , Norway, [2]Oslo Metropolitan University, Dept of Pharmacy, Oslo, Norway, [3]Section for clinical pharmacology, Dept of pharmacology, Oslo university hospital, Oslo, Norway, [4]Dept of Forensic Medicine, Oslo University Hospital, Oslo, Norway, [5]National Center for Epilepsy, Oslo University hospital, Oslo, Norway, [6]Lillehammer Hospital trust, Lillehammer, Norway

131 Extensive pharmacokinetic variability of topiramate in women of childbearing age

Aleksandra Janiga[2], MD, PhD Margrete L Burns[3], MSc Pharm Katrine Heger[2], PhD Svein I Johannessen[3,4], Professor Cecilie Johannessen Landmark[1]
[1]Oslo Metropolitan University And National Center For Epilepsy And Dept Of Pharmacology, Oslo University Hospital, , Norway, [2]Oslo Metropolitan University, Dept of Pharmacy, Oslo, Norway, [3]Section for Clinical Pharmacology, Dept of Pharmacology, Oslo University Hospital, Oslo, Norway, [4]National Center for Epilepsy, Oslo University Hospital, Oslo, Norway

132 Establishment of a quantification method for tegafur, 5-fluorouracil, and gimeracil in human plasma obtained from older adults treated with S-1

Dr. Motozumi Ando[1], Ms. Riko Seike[1], Ms. Saori Gocho[2], Ms. Shoko Maeda[2], Associate professor Norio Watanabe[1], Dr. Masami Inagaki[2], Professor Masami Kawahara[1]
[1]Department of Clinical Pharmacy and Sciences, School of Pharmacy, Aichi Gakuin University, Nagoya, Japan, [2]Department of Pharmacy, Nagoya Ekisaikai Hospital, Nagoya, Japan

133 How sure you can be of the results of quantification of psychoactive compounds in blood?

MSc Anna Lenartowicz[1], PhD Julia Mironenka[1], PhD Rafał Szewczyk[1,2], PhD Adrian Soboń[1,2], PhD Katarzyna Krupczyńska-Stopa[1,2], PhD Maciej Stopa[1,2], MSc Andrzej Kwaśnica[3]
[1]LabExperts sp. z o. o., Gdańsk, Poland, [2]Bioanalytic sp. z o. o., Gdańsk, Poland, [3]Lab4Tox sp. z o. o., Wrocław, Poland

134 Automation of sample preparation for the quantification of tacrolimus and cyclosporine in volumetric absorptive microsamples

PhD Sofia Lindahl[1], B.Sc. Karin Pettersen[1], Professor Anders Åsberg[1,2], MD PhD Karsten Midtvedt[1,2], PhD Stein Bergan[1,2], PhD Nils Tore Vethe[1]
[1]Oslo University Hospital, Oslo, Norway, [2]University of Oslo, Oslo, Norway
135 Impact of Inflammation on Intra-individual Variation in Trough Voriconazole Concentration in Patients with Hematological Malignancies
Dr. Ryota Tanaka[1], Mrs. Yu Maeda[1], Mr. Ryosuke Tatsuta[1], Dr. Kuniko Takano[2], Dr. Takehiro Hashimoto[3], Prof. Masao Ogata[2], Prof. Kazufumi Hiramatsu[3], Prof. Hiroki Itoh[1]
[1]Department of Clinical Pharmacy, Oita University Hospital, Yufu, Japan, [2]Department of Hematology, Oita University Hospital, Yufu, Japan, [3]Hospital Infection Control Center, Oita University Hospital, Yufu, Japan
136 Effect of CYP2D6 Genotype on Duloxetine Serum Concentration
Dr Kristine Hole[1,2], Dr Tore Haslemo[1,2], Prof Espen Molden[1,3]
[1]Diakonhjemmet Hospital, Oslo, Norway, [2]Oslo Metropolitan University, Oslo, Norway, [3]University of Oslo, Oslo, Norway
137 Pharmacokinetic variability and markers of toxicity of sulthiame in patients with epilepsy
Msc Pharm Katrine Heger[1], Kari Kjeldstadli[2], Nelly Ring[2], Kari Modalsli Aaberg[3], Signe Flood Kjeldsen[4], Margrete Larsen Burns[4], Svein I Johannessen[4,5], Cecilie Johannessen Landmark[1,4,5]
[1]Program for Pharmacy, Faculty of Health Sciences, Oslo Metropolitan University, Oslo, Norway, [2]Section for Clinical Pharmacology, Department of Pharmacology, Oslo University Hospital, Oslo, Norway, [3]Division of Clinical Neuroscience, National Center for Epilepsy, Oslo University Hospital, Oslo, Norway, [4]Section for Clinical Pharmacology, The National Center for Epilepsy, Department of Pharmacology, Oslo University Hospital, Oslo, Norway, [5]The National Center for Epilepsy, Oslo University Hospital, Sandvika, Norway
138 Optimising risperidone treatment in children with autism spectrum disorder: a therapeutic drug monitoring simulation study
MD Rebecca Hermans[1,2,3], BSc Alaya Storm[2], Dr. Sanne Kloosterboer[1], Prof.Dr. Manon Hillegers[1], Prof.Dr. Birgit Koch[2,3], Dr. Bram Dierckx[1], Dr. Brenda de Winter[2,3]
[1]Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Center, Rotterdam, Netherlands, [2]Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, Netherlands, [3]Rotterdam Clinical Pharmacometrics Group, Erasmus University Medical Center, Rotterdam, Netherlands
139 A pooled population pharmacokinetic study of oral and intravenous clavulanic acid in neonates
MSc Stef Schouwenburg[1,2], MD Fleur Keij[3,4], Dr. Tim Preijers[1,2], Prof. Dr. Karel Allegaert[5], Dr. Gerdien Tramper-Stranders[3], Prof. Dr. Birgit Koch[1,2]
[1]Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, Netherlands, [2]Rotterdam Clinical Pharmacometrics Group, Erasmus University Medical Centre, Rotterdam, Netherlands, [3]Department of Paediatrics, Division of Neonatology, Rotterdam, Netherlands, [4]Department of Pediatrics, Franciscus Gasthuis & Vlietland, Rotterdam, Netherlands, [5]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium
140 Preanalytical stability of 29 anti-infective agents in plasma and whole blood.
Dr Sophie Magreault[1], Dorine Pierredon[2], Judith Akinotcho - Relouzat[2], Dr Françoise Jaureguy[3], Pr Etienne Carbonnelle[3], Pr Vincent Jullien[1]
[1]Unité Fonctionelle De pharmacologie, GHU Paris Seine Saint-Denis, Ap-Hp, Université Sorbonne Paris Nord Et Sorbonne Paris Cité , Inserm, Iame , Bondy, France, [2]Unité Fonctionelle De pharmacologie, GHU Paris Seine Saint-Denis, Ap-Hp, Bondy, France, [3]Laboratoire De Microbiologie, GHU Paris Seine Saint-Denis, Ap-Hp, Université Sorbonne Paris Nord Et Sorbonne Paris Cité , Inserm, Iame, Bobigny, France
141 A Clinical Research Method for the Analysis of Antidepressant Drugs in Plasma using the Xevo TQD
Mr Stephen Balloch[1], PhD Lisa Calton[1], MSc Gareth Hammond[1], BSc Robert Wardle[1], PhD Andreas Lund Ertbjerg[2], MSc Godo Bosch[3]
[1]Waters Corporation, Wilmslow, United Kingdom, [2]Waters, Denmark, Taastrup, , [3]Waters S.A.S., Saint-Quentin En Yvelines Cedex, France

142 A Clinical Research Method for the Analysis of Immunosuppressant Drugs in Whole Blood using the Xevo TQ Absolute with Capitainer® B Devices
Mr Stephen Balloch[1], PhD Lisa Calton[1], MSc Gareth Hammond[1], BSc Robert Wardle[1], PhD Andreas Lund Ertbjerg[2], MSc Godo Bosch[3]
[1]Waters Corporation, Wilmslow, United Kingdom, [2]Waters, Denmark, Taastrup, Denmark, [3]Waters S.A.S., Saint-Quentin En Yvelines Cedex, France
143 A Simple Dilute and Shoot Method for the UPLC-MS/MS analysis of Pain Management Drugs and Drugs of Abuse from Urine for Forensic Toxicology
Mr Robert Wardle[1], Gareth Hammond[1], Mr Stephen Balloch[1], Dr Andreas Ertjberg[2], Mr Godo Bosch[3]
[1]Waters Corporation, Wilmslow, United Kingdom, [2]Waters Denmark, Taastrup, Denmark, [3]Waters S.A.S., Saint-Quentin En Yvelines Cedex, France
144 Tramadol intoxication in children: a case report
Dr Guillaume Drevin[1], Dr Antoine BAUDRILLER, Séverine FEREC, Pr Nicolas PICARD, Pr Marie BRIET, Dr Chadi ABBARA
[1]CHU Angers, Angers, France
145 What dose of clindamycin should be administered by continuous infusion during combination therapy with rifampicin? A prospective population pharmacokinetics study.
Leo Mimram[1], Dr Sophie Magreault[2], Dr Younes Kerroumi[3], Dr Dominique Salmon[4], Dr Benjamin Kably[5], Dr Simon Marmor[3], Dr Anne-Sophie Jannot[6], Pr Vincent Jullien[2], Dr Valerie Zeller[7]
[1]Unité Fonctionnelle de Pharmacologie, GHU Paris Seine Saint-Denis, AP-HP, Bondy, France, [2]Unité Fonctionelle de Pharmacologie, GHU Paris Seine Saint-Denis, AP-HP, Université Sorbonne Paris Nord Et Sorbonne Paris Cité , Inserm, Iame, , France, [3]Centre de Référence des Infections Ostéo-Articulaires Complexes (CRIOAC), Groupe Hospitalier Diaconesses–Croix Saint-Simon, Paris, France, [4]Service de Médecine Interne, Hôpital Cochin, Assistance Publique–Hôpitaux de Paris (APHP), Paris, France, [5]Service de Pharmacologie DMU BioPhyGen, Hôpital Européen Georges-Pompidou, APHP, Paris, France, [6]Service d'Informatique Médicale, Biostatistiques et Santé Publique, Hôpital Européen Georges-Pompidou, APHP, Paris, France, [7]Service de Médecine Interne et Infectiologie, Groupe Hospitalier Diaconesses–Croix Saint-Simon, Paris, France
146 Routine Therapeutic Drug Monitoring of Rivaroxaban:
Experience at a Tertiary Center
Dr Paul Chin[1,2], Dr Adele O'Mahoney[2], Dr Isabel Hiskett[2]
[1]University Of Otago, Christchurch, New Zealand, [2]Te Whatu Ora Health New Zealaand - Waitaha Canterbury, Christchurch, New Zealand
147 Clozapine treatment individualization: a joint pharmacokinetic/pharmacogentic approach
Dr Chadi Abbara[1], Dr Guillaume Drevin[1], Dr Guillaume Ifrah[2], Pr Nicolas Picard[3], Pr Bénédicte Gohier[2], Pr Marie Briet[1]
[1]Angers University Hospital - Pharmacology and Toxicology department, Angers, France, [2]Angers University Hospital - Psychiatry department, Angers, France, [3]Limoges University Hospital - Pharmacology and Toxicology department, Limoges, France
148 A comparison of free concentrations and fractions in vivo between unchanged form and active metabolite of itraconazole using UHPLC-MS/MS assay with equilibrium dialysis.
Mr. Motoshi Iwao[1], Dr. Ryota Tanaka[1], Dr. Yosuke Suzuki[2], Mr. Ryosuke Tatsuta[1], Dr. Takehiro Hashimoto[3], Prof. Kazufumi Hiramatsu[3], Prof. Hiroki Itoh[1]
[1]Department of Clinical Pharmacy, Oita University Hospital, Hasama-machi, Japan, [2]Department of Medication Use Analysis and Clinical Research, Meiji Pharmaceutical University, Kiyose, Japan, [3]Hospital Infection Control Center, Oita University Hospital, Hasama-machi, Japan
149 Simultaneous detection of blood concentration of CDK4/6 inhibitors and P-gp genetic polymorphism from a single dried blood spot
Dr Kei Irie[1,2], Mr Naoto Masuda[2], Dr Shuji Kishimoto[2], Dr Nobuyuki Muroi[1,3], Dr Tohru Hashida[1,2], Dr Shoji Fukushima[2]
[1]Department of Clinical Pharmacy Research, Center for Clinical Research and Innovation, Kobe City Medical Center General Hospital, Kobe, Japan, [2]Faculty of Pharmaceutical Science, Kobe Gakuin University, Kobe, Japan, [3]Department of Pharmacy, Kobe City Medical Center General Hospital, Kobe, Japan

150 Clinical consequences of infliximab immunogenicity and the impact of therapeutic drug monitoring: secondary analyses of a randomised clinical trial

MD Marthe Kirkesæther Brun[1,2], MD Kristin Hammersbøen Bjørlykke[2,3], MD, PhD Johanna E. Gehin[4], PhD David John Warren[4], PhD Rolf A. Klaasen[4], PhD Joseph Sexton[1], MD, PhD Øystein Sandanger[5], Prof Tore K. Kvien[1,2], MD, PhD Cato Mørk[6], Prof. Jørgen Jahnsen[2,3], MD, PhD Nils Bolstad[4], MD, PhD Kristin Kaasen Jørgensen[3], Prof. Espen A. Haavardsholm[1,2], MD, PhD Guro Løvik Goll[1], MD, PhD Silje Watterdal Syversen[1]

[1]Center for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, Oslo, Norway, , Norway, [2]Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [3]Department of Gastroenterology, Akershus University Hospital, Lørenskog, Norway, [4]Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway, [5]Section of Dermatology, Oslo University Hospital, Oslo, Norway, [6]Akershus Dermatology Center, Oslo, Norway

151 Development and validation of a method for the quantification of multi-class pesticides in hair by liquid chromatography - mass spectrometry

Eloïse Brillard[2], Camille Larrue[2], Antoine Dupuis[2,3], Pharmd, Phd Sandrine Lefeuvre[1,2]

[1]Laboratory of Toxicology and Pharmacokinetic , CHU Poitiers, INSERM CIC 1402, Poitiers, France, [2]CNRS 7267 EBI, University of Poitiers, Poitiers, France, [3]Pharmacy, CHU Poitiers, INSERM CIC 1402, Poitiers, France

152 Population Pharmacokinetics and Dosing Optimization of Ceftazidime in Term Asphyxiated Neonates during Controlled Therapeutic Hypothermia

Msc Marlotte van der Veer[1], Timo de Haan[2], Linda Franken[1], Caspar Hodiamont[3], Floris Groenendaal[11], Peter Dijk[4], Willem de Boode[5], Sinno Simons[6], Koen Dijkman[7], Henrica van Straaten[8], Monique Rijken[9], Filip Cools[10], Debbie Nuytemans[2], Anton van Kaam[2], Yuma Bijleveld[1], Ron Mathôt[1]

[1]Department of Hospital Pharmacology & Clinical Pharmacology, Amsterdam University Medical Center, Amsterdam, Netherlands, [2]Department of Neonatology Emma Children's Hospital, Amsterdam University Medical Center,, , Amsterdam, Netherlands, [3]Medical Microbiology, Amsterdam University Medical Center, Amsterdam, Netherlands, [4]University Medical Center Groningen, Beatrix Children's Hospital, Department of Pediatrics, Division of Neonatology, Gronigen, Netherlands, [5]Department of Neonatology, Radboud University Medical Center, Radboud Institute for Health Sciences, Amalia Children's Hospital, Nijmegen, Netherlands, [6]Department of Pediatrics, Division of Neonatology, Erasmus MC-Sophia Children's Hospital, Rotterdam, Netherlands, [7]Department of Neonatology, Máxima Medical Center Veldhoven, Veldhoven, Netherlands, [8]Department of Neonatology, Isala Clinics, Zwolle, Netherlands, [9]Department of Neonatology, Leiden University Medical Center, Leiden, Netherlands, [10]Department of Neonatology, Vrije Universiteit Brussel, Brussels, Belgium, [11]Department of Neonatology, Wilhelmina Children's Hospital, Utrecht, Netherlands

153 Double absorption gamma model for mycophenolic acid and systemic lupus erythematosus pediatric patients using a stochastic approximation expectation-maximization algorithm

PharmD Kévin Koloskoff[1], PhD Lucie Chambon[2], PhD Sylvain Benito[2], MD PhD Evelyne Jacqz-Aigrain[3], PharmD PhD Jean-Baptiste Woillard[1]

[1]Inserm, University of Limoges, CHU Limoges, P&T, U1248, France, [2]Exactcure, , France, [3]Université Paris Cité, Department of Pharmacology and Pharmacogenetics, France

154 Quetiapine galore? Doses, diagnoses and serum concentrations of Norwegian quetiapine users 2001-2019 in a therapeutic drug monitoring material

Mr. Håvard Breivik[1,2], Dr. Andreas Austgulen Westin[2,1], Professor Lars Slørdal[1,2], Dr. Joachim Frost[2,1]

[1]Norwegian University of Science and Technology, Trondheim, Norway, [2]St. Olav University Hospital, Trondheim, Norway

155 Predictive Performance of a Gentamicin Pharmacokinetic Model in Term Asphyxiated Neonates undergoing Controlled Therapeutic Hypothermia

Msc Marlotte van der Veer[1], Timo de Haan[2], Linda Franken[1], Floris Groenendaal[3], Peter Dijk[4], Willem de Boode[5], Sinno Simons[6], Koen Dijkman[7], Henrica van Straaten[8], Monique Rijken[9], Filip Cools[10], Debbie Nuytemans[2], Anton van Kaam[2], Yuma Bijleveld[1], Ron Mathôt[1]

[1]Department of Hospital Pharmacology & Clinical Pharmacology, Amsterdam UMC location University of Amsterdam, , Netherlands, [2]Department of Neonatology, Emma Children's Hospital, Amsterdam

University Medical Center, Amsterdam, The Netherlands, [3]Department of Neonatology, Wilhelmina Children's Hospital, Utrecht, The Netherlands, [4]University Medical Center Groningen, Beatrix Children's Hospital, Department of Pediatrics, Division of Neonatology, University of Groningen, Groningen, The Netherlands, [5]Department of Neonatology, Radboud University Medical Center, Radboud Institute for Health Sciences, Amalia Children's Hospital, Nijmegen, The Netherlands, [6]Department of Pediatrics, Division of Neonatology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands, [7]Department of Neonatology, Máxima Medical Center Veldhoven, Veldhoven, The Netherlands, [8]Department of Neonatology, Isala Clinics, Zwolle, The Netherlands, [9]Department of Neonatology, Leiden University Medical Center, Leiden, The Netherlands, [10]Department of Neonatology, Vrije Universiteit Brussel, Belgium

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Personalized tacrolimus dosage by model-based Bayesian Prediction in renal transplant recipients. A prospective controlled randomized clinical trial.

Dr Nuria Lloberas[1], Prof Pharm D PhD Helena Colom[2], PhD Anna Vidal-Alabró[1], PhD Pere Fontova[1], PhD Raul Rigo[3], PhD Ariadna Padró[3], MD PhD Edoardo Melilli[1], MD PhD Núria Montero[1], MD PhD Ana Coloma[1], MD PhD Anna Manonelles[1], MD PhD Alex Favà[1], MD PhD Oriol Bestard[1], MD PhD Maria Meneghini[1], MD PhD Joan Torras[1], Prof MD PhD Josep M Cruzado[1], Prof MD PhD Josep M Grinyó[1]
[1]Nephrology Service, Bellvitge University Hospital - IDIBELL, Barcelona, Spain, [2]Department of Pharmacy and Pharmaceutical technology and Physical-chemistry, Biopharmaceutics and Pharmacokinetics Unit, School of Farmacy and Food Sciences, University of Barcelona, Barcelona, Spain, [3]Biochemistry Department,Bellvitge University Hospital - IDIBELL, Barcelona, Spain

158 Real-life pharmacokinetic data of mycophenolic acid and model based calculation of area-under-the-curve in a pediatric population with different renal diseases

Carsten Müller[1], PhD Pedram Omrani[1,2], Dr. Silke Gastine[4], Dr. Agnes Hackl[2], Dr. Nieko Punt[5], Prof. Martin Hellmich Hellmich[3], MD Rasmus Ehren[2], MD Martin H. J. Wiesen[1], Prof. Lutz T Weber[2]
[1]Pharmacology at the Laboratory Diagnostics Centre, Department of Therapeutic Drug Monitoring, University Hospital of Cologne, Cologne, Germany, [2]Pediatric Nephrology, Children's and Adolescents' Hospital, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany, [3]Institute of Medical Statistics and Computational Biology, Faculty of Medicine and University Hospital Cologne, Cologne, Germany, [4]Great Ormond Street Institute of Child Health, University College London, London, United Kingdom, [5]Medimatics, 6229 HR Maastricht, The Netherlands University Medical Center Groningen, Department of Clinical Pharmacy, Maastricht, The Netherlands

159 Comparison of three renal function formulas for Ganciclovir/Valganciclovir dose individualization using a population approach in CMV transplant patients

PhD Panagiotis Nikolaos Lalagkas[2], PhD Jorge Iliou[2], PhD Raul Rigo[3], MD PhD Oriol Bestard[1], Prof MD PhD Josep M Cruzado[1], MD PhD Edoardo Melilli[1], MD PhD Joan Torras[1], PhD Beatriz Fernández-Alarcon[2], Prof MD PhD Josep M Grinyó[1], Prof PhD Helena Colom[2], Dr NURIA LLOBERAS[1]
[1]Nephrology Service, Bellvitge University Hospital - IDIBELL, Barcelona, Spain, [2]Department of Pharmacy and Pharmaceutical technology and Physical-chemistry, Biopharmaceutics and Pharmacokinetics Unit, School of Farmacy and Food Sciences, University of Barcelona, Barcelona, Spain, [3]Biochemistry Department,Bellvitge University Hospital - IDIBELL, Barcelona, Spain

160 Paracetamol (Acetaminophen) and Metabolites Population Pharmacokinetics Model in children and adults with Spinal Muscular Atrophy

MSc Qiaolin Zhao[1,2], MD Marie Mostue Naume[3,4], MD Sissel Sundell Haslund-Krog[5], Dr. Thomas Krag[3], Dr. Brenda C.M. de Winter[1,2], MD Karoline Lolk Revsbeck[3], Prof. John Vissing[3], Dr. Helle Holst[5], Dr. Morten Hylander Møller[6], Dr. Morten Morten[7], MD Christina Engel Høi-Hansen[4], Dr. Alfred Peter Born[4], Dr. Per Bo Andersen[4], MD Mette Cathrine Ørngreen[3,4], Brenda d Winter
[1]Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, Netherlands, [2]Rotterdam Clinical Pharmacometrics Group, Erasmus Univerity Medical Center, Rotterdam, Netherlands, [3]Copenhagen Neuromuscular Center, Department of Neurology, University Hospital of Copenhagen, Copenhagen, Denmark, [4]Department of Pediatric and Adolescent Medicine, University Hospital of Copenhagen, Copenhagen, Denmark, [5]Department of Clinical Pharmacology, Bispebjerg

Hospital, Copenhagen, Denmark, [6]Department of Intensive Care, Copenhagen University Hospital, Copenhagen, Denmark, [7]Department of Clinical Genetics, Copenhagen University Hospital, Copenhagen, Denmark

161 The importance of model selection for a priori model informed precision dosing of vancomycin

PharmD PhD Sebastiaan Sassen[1,2,4], PharmD Bram Agema[1,2,3], Mr. Tolra Kocher[1], PharmD PhD Brenda de Winter[1,2,4], PharmD PhD Birgit Koch[1,2,4]

[1] Dept. of Clinical Pharmacy, Erasmus University Medical Center, Rotterdam, Netherlands, [2]Rotterdam Clinical Pharmacometrics Group, Rotterdam, The Netherlands, [3]Dept. of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands, [4]Center for Antimicrobial Treatment Optimization Rotterdam, Rotterdam, The Netherlands

162 Dual channel LC-MS/MS for quantification of four immunosuppressants in whole blood for therapeutic drug monitoring

Ms Tanja Zijp[1,2], Mr Kai Van Hateren[1], Mr Hiltjo Kuiper[1], Mr Erwin Jongedijk[1], prof.dr. Daan Touw[1,2]

[1]UMCG, Groningen, Netherlands, [2]University of Groningen, Groningen, The Netherlands

164 Pharmacogenetic-guided Management of Fluoropyrimidines Dosing in DPYD Compound Heterozygosis

Dr. Giammarco Baiardi[1,2], MD Manuela Stella[1,2], MD Fabio Piras[1,2], Alessia Cafaro[2,3], MD Matteo Clavarezza[4], Stefania Casazza[5], Andrea Decensi[4], Prof. Francesca Mattioli[1,2]

[1]Clinical Pharmacology Unit, Ente Ospedaliero Ospedali Galliera, Genoa, Italy, [2]Department of Internal Medicine, Pharmacology & Toxicology Unit, University of Genoa, Genoa, Italy, [3]Chromatography and Mass Spectrometry Section, Central Laboratory of Analysis, IRCCS Istituto Giannina Gaslini, Genoa, Italy, [4]Medical Oncology Unit, Ente Ospedaliero Ospedali Galliera, Genoa, Italy, [5]Pathology Unit, Ente Ospedaliero Ospedali Galliera, Genoa, Italy

165 Strengthening Chemical Risk Assessment through the Development of Adverse Outcome Pathways for Immunotoxicity Endpoints

Nicola Smith, Marcin Wojewodzic, Karine Bø, Hubert Dirven, Birgitte Lindeman[1]

[1]Norwegian Institute of Public Health, Oslo, Norway

167 Etanercept (ETN) treatment of adenosine deaminase 2 deficiency (DADA2) for the prevention of ischemic events and the inflammatory biomarkers improvement: a case report.

Giorgia Babaglioni[1], Pharmacist Lorenzo Silva[1], Hospital Pharmacist Elena Festa[1], Hospital Pharmacist Daniela Paganotti[1], Phisician Francesca Crisafulli[2], Phisician Paolo Airò[2], Head Hospital Pharmacy Tullio Elia Testa[1], Head Rheumatology and Clinical Immunology Unit Franco Franceschini[2]

[1]ASST Spedali Civili of Brescia, Hospital Pharmacy, Brescia, Italy, [2]ASST Spedali Civili of Brescia, Rheumatology and Clinical Immunology Unit, Brescia, Italy

168 Use of Dupilumab in the treatment of bullous pemphigoid: a case report.

Lorenzo Silva[1], Pharmacist Giorgia Babaglioni[1], Pharmacist Chiara Galuppi[1], Hospital Pharmacist Elena Festa[1], Head Hospital Pharmacist Tullio Elia Testa[1], Phisician Vincenzo Maione[2], Hospital Pharmacist Daniela Paganotti[1]

[1]ASST Spedali Civili of Brescia, Hospital Pharmacy, Brescia, Italy, [2]ASST Spedali Civili of Brescia, Dermatology, Brescia, Italy

169 Pharmacokinetic Evaluation of Oral Viscous Budesonide in Pediatric Patients with Eosinophilic Esophagitis in Repaired Esophageal Atresia

PhD Raffaele Simeoli[1], Sara Cairoli[1], MD Marco Roversi[2], MD Renato Tambucci[3], MD Luigi Dall'Oglio[4], MD Carlo Dionisi Vici[1], MD Giuseppe Pontrelli[5], MD, PhD Oscar Della Pasqua[6], MD Paola De Angelis[3], Bianca Maria Goffredo[1]

[1]Division of Metabolic Diseases and Drug Biology, Bambino Gesù Children's Hospital IRCCS, Rome, Italy, [2]Residency School of Pediatrics, University of Rome Tor Vergata, Rome, Italy, [3]Digestive Endoscopy Unit, Bambino Gesù Children's Hospital IRCCS, Rome, Italy, [4]Digestive Endoscopy and Surgery Unit, Bambino Gesù Children's Hospital IRCCS, Rome, Italy, [5]Centre of Excellence for the development and implementation of medicines, vaccines, and medical devices for pediatric use, Bambino Gesù Children's Hospital IRCCS, Rome, Italy, [6]University College London, London, United Kingdom

170 Local experience on adalimumab and etanercept biosimilar drugs: safety and efficacy confirmation encourages rheumatologist biosimilar prescription.
Giorgia Babaglioni[1], Pharmacist Lorenzo Silva[1], Hospital Pharmacist Elena Festa[1], Hospital Pharmacist Daniela Paganotti[1], Head of Hospital Pharmacy Tullio Elia Testa[1], Head of Rheumatology and Clinical Immunology Unit Franco Franceschini[2]
[1]ASST Spedali Civili of Brescia, Hospital Pharmacy, Brescia, Italy, [2]ASST Spedali Civili of Brescia, Rheumatology and Clinical Immunology Unit, Brescia, Italy
171 Liposomal Amphotericin B consumption in intensive care units (ICUs) from 2018 to 2021.
Lorenzo Silva[1], Pharmacist Giorgia Babaglioni[1], Hospital pharmacist Elena Festa[1], Head hospital pharmacist Tullio Elia Testa[1], Hospital Pharmacist Daniela Paganotti[1]
[1]ASST Spedali Civili of Brescia, Hospital Pharmacy, Brescia, Italy
172 High-throughput UPLC-ESI-MS/MS method for the determination of Phosphatidylethanol (PEth) 16:0/18:1 in whole blood: the clinical application
Dr. Linda Sanderson[1]
[1]Karolinska Universitetssjukhuset, Huddinge, Sverige
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Sara Cairoli[1], PhD Raffaele Simeoli[1], MD Marcella Greco[2], Alessia Vitale[1], Giacomo Antonetti[1], Alessandro Mancini[1], Bianca Maria Goffredo[1]
[1]Division of Metabolic Diseases and Drug Biology, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, [2]Division of Nephrology, Bambino Gesù Children's Hospital IRCCS, Rome, Italy
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[1]Angers University Hospital - Pharmacology and Toxicology department, Angers, France, [2]Angers University Hospital - Blood Diseases department, Angers, France, [3]Cancer University Institut Oncolpole, Toulouse, France, [4]Grenoble Alpes University, Grenoble, France, [5]Angers University - UFR Santé, Angers, France
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[1]Clinical and Experimental Pharmacology Unit, Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy, , , [2]IRCCS Mondino Foundation, Pavia, Italy. Member of ERN-Epicare, , Italy, [3]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, [4]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy, [5]Institute for Molecular and Translational Cardiology (IMTC), San Donato Milanese, , Italy, [6]B.S.N. srl R&D Laboratory, Castelleone, Italy, , , [7]Associazione Farmaceutici dell'Industria (AFI), Milan, Italy, ,
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[1]Labexperts sp z o.o., Gdansk, Poland, [2]Bioanalytic sp z o.o., Gdansk, Poland, [3]Medical University of Gdansk, Gdansk, Poland
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[1]Department of Pharmaceutical Analysis and Nuclear Pharmacy, Faculty of Pharmacy, Comenius University in Bratislava, Bratislava, Slovakia, [2]Toxicological and Antidoping Center, Faculty of

Pharmacy, Comenius University in Bratislava, Bratislava, Slovakia, [3]Department of Galenic Pharmacy, Faculty of Pharmacy, Comenius University in Bratislava, Bratislava, Slovakia

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PharmDr. Ivana Čižmárová[1,2], prof. RNDr. PhD. Peter Mikuš[1,2], Assoc. prof. PharmDr. PhD. Juraj Piešťnaský[2,3]

[1]Department of Pharmaceutical Analysis and Nuclear Pharmacy, Faculty of Pharmacy, Comenius University in Bratislava, Bratislava, Slovakia, [2]Toxicological and Antidoping Center, Faculty of Pharmacy, Comenius University in Bratislava, Bratislava, Slovakia, [3]Department of Galenic Pharmacy, Faculty of Pharmacy, Comenius University in Bratislava, Bratislava, Slovakia

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Bruno Casetta[1], Dr Michele Senatore[2], Dr Antonio Martini[3], Dr Sara Marzatico[1], Dr Gianluca Gazzaniga[4], Dr Sergio Finazzi[3], Prof Adriana Pani[5], Prof Frasncesco Scaglione[5]

[1]BSN, Castelleone, Italy, [2]Chemical-Clinical Analyses, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy, [3]Biochemistry Lab., ASST Ovest Milanese, Legnano Hospital, Legnano, Italy, [4]School of Clinical Pharmacology and Toxicology, Università degli Studi, Milano, Italy, [5]Department of Oncology and Hemato-Oncology, Università degli Studi , Milano, Italy, [6]Chemical-Clinical and Microbiological Analyses, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy

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PharmDr. Eliška Maraczek Marková[1,2], PharmDr. Bc. PhD. Kateřina Horská[1,2], PharmDr. MBA Šárka Kozáková[1,3]

[1]Department of Clinical Pharmacy, Hospital Pharmacy, The University Hospital Brno, Brno, Czech Republic, [2]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Masaryk University, Brno, Czech Republic, [3]Department of Pharmacology, Faculty of Medicine, Masaryk University, Brno, Czech Republic

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Bianca Maria Goffredo[1], MD Marco Marano[2], MD Isabella Guzzo[3], MD Andrea Cappoli[3], MD Raffaella Labbadia[3], Sara Cairoli[1], Chiara Rossi[1], PhD Raffaele Simeoli[1], MD Gabriella Bottari[2]

[1]Division of Metabolic Diseases and Drug Biology, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, [2]Pediatric Intensive Care Unit, Department of Emergency, Acceptance and General Pediatrics, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, [3]Department of Pediatrics, Division of Nephrology and Dialysis, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

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Dr Marie-Clémence Verdier[1], Dr Charles Maurille[2], Dr Christian Creveuil[3], Dr Aurélie Baldolli[2], Pr Renaud Verdon[2,4], Bénédicte Franck[1], Emmanuelle Comets[1]

[1]Univ Rennes, CHU Rennes, Department of Pharmacology, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, F-35000 Rennes, , France, [2]Normandie Univ, UNICAEN, CHU de Caen Normandie, Department of Infectious Diseases, , , France, [3]Normandie Univ, UNICAEN, CHU de Caen Normandie, Department of Biostatistics and Clinical Research, 14000 Caen , , France, [4]INSERM U1311 DynaMicURe, Normandie University, UNICAEN, UNIROUEN, 14000 Caen , , France

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MSc Agnieszka Czajkowska[1], MSc Marta Górska[1], MSc MPharm Arkadiusz Kocur[1,2]

[1]Pharmacokinetics Laboratory, Children's Memorial Health Institute, Warsaw, Poland, [2]Department of Drug Chemistry, Medical University of Warsaw , Warsaw, Poland

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[1]Sanquin Diagnostic Services, Amsterdam, Netherlands, [2]Department of Neurology, MS Center Amsterdam, Amsterdam UMC Location VUMC, Amsterdam, Netherlands, [3]Department of Epidemiology and Data Science, Vrije Universiteit Amsterdam, Amsterdam, Netherlands
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[1]Amsterdam UMC, Amsterdam, The Netherlands, [2]UMC Utrecht, Utrecht, The Netherlands, [3]Hospital Gelderse Vallei, Ede, The Netherlands, [4]St. Antonius Hospital, Nieuwegein, The Netherlands, [5]Noord west Hospital, Alkmaar, The Netherlands, [6]Elizabeth Tweesteden Hospital, Tilburg, The Netherlands, [7]Spaarne Gasthuis, Hoofddorp, The Netherlands, [8]OLVG, Amsterdam, The Netherlands, [9]Jeroen Bosch Hospital, Den Bosch, The Netherlands, [10]Bravis Hospital, Roozendaal, The Netherlands
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[1]Amsterdam UMC, Amsterdam, Netherlands, [2]UMC Utrecht, Utrecht, The Netherlands, [3]Hospital Gelderse Vallei, Ede, The Netherlands, [4]St Antonius Hospital, Nieuwegein, The Netherlands, [5]Noord West Hospital, Alkmaar, The Netherlands, [6]Elisabeth Tweesteden Hospital, Tilburg, The Netherlands, [7]Spaarne Gasthuis, Hoofddorp, The Netherlands, [8]OLVG, Amsterdam, The Netherlands, [9]Jeroen Bosch Hospital, Den Bosch, The Netherlands, [10]Bravis Hospital, Roozendaal, The Netherlands
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[1]Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, The Netherlands, [2]Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Center, Rotterdam, The Netherlands, [3]Rotterdam Clinical Pharmacometrics Group, Erasmus University Medical Center, Rotterdam, The Netherlands, [4]Department of clinical chemistry, Erasmus MC, University Medical Center, , The Netherlands
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[1]Department of Experimental and Clinical Toxicology, Institute of Experimental and Clinical Pharmacology and Toxicology, Center for Molecular Signaling (PZMS), Saarland University, Homburg, Germany , [2]Karolinska Institute, Clinical Neuroscience , Stockholm, Sweden
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[1]Department of Clinical Pharmacy, University Medical Center Utrecht/Wilhelmina Children's Hospital, Utrecht, the Netherlands, [2]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands, [3]Department of

Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, the Netherlands, [4]Department of Hematology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands, [5]Department of Data Science and Biostatistics, Julius Center for Health Sciences and Primary Care, Utrecht, the Netherlands, [6]Center for Translational Immunology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

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Amandine Etcheverry[2], Regis Bouvet[2], Florent Denoual[2], Christele Dubourd[2], Marie-Clémence Verdier[1], Marie-Dominique Galibert[2], Dr Camille Tron[1]

[1]Pharmacology department, Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) UMR_S 1085, F-35000 Rennes, France, Rennes, France, [2]Department of Molecular Genetics and Genomics, Rennes Hospital University, Rennes, France., Rennes, France

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Kajie Liang[1], PharmD, PhD L.L. Krens[1], MD, PhD J.J.B. van der Vlugt[2], PharmD, PhD T.M. Bosch[1,3]

[1]Department of Hospital Pharmacy, Maasstad Hospital, Rotterdam, The Netherlands, [2]Antes Parnassia Group, Psychiatric Hospital, Rotterdam, The Netherlands, [3]Department of Clinical Pharmacology & Toxicology MaasstadLab, Maasstad Hospital, Rotterdam, The Netherlands

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MD Henrik Magistad Knutrud[1]

[1]Department of Clinical Pharmacology, Oslo University Hospital, Oslo , Norway

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Mr Olivier Le Tilly[1], Mrs Caroline Dartigeas[1], Mr David Ternant[1]

[1]CHRU de Tours, Université de Tours, Tours, France

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[1]University Hospital of Rennes, Laboratory of Clinical Pharmacology, 35000 Rennes, France, Rennes, France, [2]University Hospital of Rennes, Department of infectious diseases, 35000 Rennes, France, Rennes, France

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[1]Department of Medical Biochemistry and Pharmacology, Bergen, Norway, [2]Department of Clinical Science, University of Bergen, Bergen, Norway, [3]Neuro-SysMed, Department of Neurology, Haukeland University Hospital, Bergen, Norway, [4]Department of Clinical Medicine, University of Bergen, Bergen, Norway, [5]Computational Biology Unit, Department of Informatics, University of Bergen, Bergen, Norway

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Dr András Füredi[1,2], Dóra Bereczki[1,2,3], Balázs Gombos[2], Ines Lidia Haffaressas[2], Dr Pál Szabó[4], Dr Péter Vajdovich[5], Dr Péter Fürjes[1]

[1]Microsystems Laboratory, Centre For Energy Research, Institute Of Technical Physics And Materials Science, Budapest, Hungary, [2]Institute of Enzymology, Research Centre for Natural Sciences, Budapest, Hungary, [3]Doctoral School on Materials Sciences and Technologies, Óbuda University, Budapest, Hungary, [4]Centre for Structural Sciences, Research Centre for Natural Sciences, Budapest, Hungary, [5]Department of Clinical Pathology and Oncology, University of Veterinary Medicine, Budapest, Hungary

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Drs. Amy Rieborn[1], dr. Tom van der Hulle[2], prof. dr. Hans Gelderblom[2], prof. dr. Teun van Gelder[1], dr. Dirk Jan Moes[1]

[1]Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, Netherlands, [2]Department of Medical Oncology, Leiden University Medical Center, Leiden, Netherlands

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[1]Sanquin Diagnostic Services, Amsterdam, the Netherlands, [2]Amsterdam Rheumatology and Immunology Center, location Reade, Department of Rheumatology, Amsterdam, the Netherlands, [3]3. Department of immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, Amsterdam, the Netherlands
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[1]University of Utah / ARUP Laboratories, , United States
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[1]ASST Spedali Civili Brescia, Brescia, Italy, [2]ASST Fatebenefratelli Sacco, Milano, Italy, [3]Università degli studi di Milano, Milano, Italy
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[1]ACFT, University of Calgary, Calgary, Canada
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[1]University College London, London, United Kingdom, [2]University of Tartu, Tartu, Estonia, [3]Epilepsy Society, Chalfont St Peter, United Kingdom
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[1]Nagoya University Hospital, Nagoya, Japan
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[1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, South Korea, [2]Department of Clinical Pharmacology and Therapeutics, Seoul National University Bundang Hospital, Seongnam, South Korea, [3]Department of Pharmacy, Wonkwang University College of Pharmacy, Iksan, South Korea
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[1]Mayo Clinic Arizona, Phoenix, United States
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[1]Division of Pharmaceutical Care Sciences, Keio University Graduate School of Pharmaceutical Sciences, Tokyo, Japan, [2]Division of Pharmaceutical Care Sciences, Center for Social Pharmacy and Pharmaceutical Care Sciences, Keio University Faculty of Pharmacy, Tokyo, Japan, [3]Department of Pharmacy, National Center for Child Health and Development, Tokyo, Japan, [4]Organ Transplantation Center, National Center for Child Health and Development, Tokyo, Japan
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Msc Fenna de Vries[1,2], Msc Leila-Sophie Otten[2], PhD Rob ter Hein[2], PhD Floris Loeff[3], Msc Lindsey te Brake[2], PhD Eric Franssen[1]
[1]Department of Pharmacy, OLVG, , Amsterdam, The Netherlands, [2]Department of Pharmacy, Radboudumc, Nijmegen, The Netherlands, [3]Sanquin Diagnostic Services, Amsterdam, The Netherlands
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[1]St. Olavs hospital, Trondheim University Hospital, Trondheim, Norway, [2]Department of Clinical and Molecular Medicine (IKOM), Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Trondheim, Norway
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[1]Department of Pharmacy, Kobe University Hospital, Kobe, Japan, [2]Department of Forensic Medicine and Clinical Toxicology, Assiut University, Graduate School of Medicine, Assiut, Egypt, [3]Education and Research Center for Clinical Pharmacy, Kobe Pharmaceutical University, Kobe, Japan, [4]Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan
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[1]Rennes University Hospital, Rennes, France, [2]Cliniques Universitaires Saint-Luc, UC Louvain, Brussels, Belgium, [3]CHU Nantes, Nantes, France, [4]Centre Hospitalo-Universitaire Caen-Normandie, Caen, France, [5]IFB, Hôpital Purpan, Toulouse, France, [6]CHU de Dijon, Dijon, France, [7]Université de Lorraine, CNRS, IMoPA, Nancy, France
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[1]Peking University Third Hospital, Beijing, China
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[1]Microsystems Laboratory, Institute of Technical Physics and Materials Science, Centre for Energy Research, Budapest, Hungary, [2]Doctoral School on Materials Sciences and Technologies, Óbuda University, Budapest, Hungary, [3]Institute of Enzymology, Research Centre for Natural Sciences, Budapest, Hungary
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[1]Medical University of Warsaw, Department of Drug Chemistry, Warsaw, Polska
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[1]Clinical Pharmacy Center, Department of Pharmacy, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, China, [2]Key Laboratory of Endocrine Gland Diseases of Zhejiang Province, Hangzhou, China
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[1]Zhejiang Provincial People's Hospital, Hangzhou, China, [2]Key Laboratory of Endocrine Gland Diseases of Zhejiang Province, Hangzhou, China

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[1]Center For Psychopharmacology, , Norway
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[1]School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences & Technology, Baddi, India, [2]Faculty of Pharmacy, Jamia Hamdard, Hamdard Nagar, India
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[1]Clinical and Experimental Pharmacology Unit, Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, , Italy, [2]IRCCS Mondino Foundation, Pavia, Italy. Member of ERN-Epicare, , Italy, [3]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, , , [4]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy, , , [5]Institute for Molecular and Translational Cardiology (IMTC), San Donato Milanese, Milan, Italy, , , [6]Associazione Farmaceutici dell'Industria (AFI), Milan, , Italy
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[1]Department of Experimental and Clinical Toxicology, Saarland University, Homburg, Germany, [2]Department of Gynaecology, Obstetrics and Reproductive Medicine, Saarland University Hospital, Homburg, Germany
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[1]Rennes University Hospital, Rennes, France, [2]Cliniques Universitaires Saint-Luc, UCLouvain, Brussels, Belgium, [3]Limoges University Hospital, Limoges, France, [4]Lille University Hospital, Lille, France, [5]Brest University Hospital, Brest, France
228 Detection of kidney transplant patients at risk to lose their graft: neural networks and interpretability
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[1]Inserm, Pharmacology & Toxicology, U1248, Limoges, France, [2]Department of Transplantation Medicine, Oslo Universitary Hospital, Oslo, Norway
229 Simplified pharmacokinetic interaction study utilizing capillary microsampling performed by patients themselves – patiromer effect on tacrolimus
Professor Anders Åsberg[1,2], Dr Rasmus Kirkeskov Carlsen[1], Dr Nils Tore Vethe[3], MSc(pharm) Shadi Alipour[1], Dr Karsten Midtvedt[1], Dr Geir Mjøen[1]
[1]Department of Transplantation Medicine, Oslo University Hospital – Rikshospitalet, Oslo, Norway, [2]Department of Pharmacy, University of Oslo, Oslo, Norway, [3]Department of Pharmacology, Oslo University Hospital – Rikshospitalet, Oslo, Norway
230 Intraindividual variability in absolute bioavailability and clearance of midazolam in healthy individuals
Dr Kine E Kvitne[1], MSc Ole Martin Drevland[1], MSc Nora Haugli[1], MSc Eline Skadberg[1], Dr Hasse Khiabani Zaré[2], Dr Anders Åsberg[1,3], Dr Ida Robertsen[1]

[1]Department of Pharmacy, University of Oslo, Oslo, Norway, [2]Department of Pharmacology, Oslo University Hospital, Oslo, Norway, [3]Department of Transplant Medicine, Oslo University Hospital, Oslo, Norway

231 A fast and simple test for amatoxins in human urine – Comparison of a lateral flow immunoassay with LC-HRMS/MS analysis

Aline Christin Vollmer[1], Thomas P Bambauer[1,2], Candace S Bever[3], Dr Lea Wagmann[1], Prof. Dr. Markus R Meyer[1]

[1]Departement of Experimental and Clinical Toxicology, Saarland University, Homburg, Germany, [2]Departement of Forensic Toxicology, Goethe University, Frankfurt, Germany, [3]Foodborne Toxin Detection and Prevention Research Unit, Department of Agriculture, Agricultural Research Service, Western Regional Research Center, Albany, United States of America

232 Detection of dichlorobisphenol-A (DCBPA) in hair following a single dose to female volunteers. A proof-of-concept study to demonstrate the interest of hair as a biomarker of exposure to endocrine disrupting compounds.

Julien Robin[1,2,3], PhD student Noémie Plattard[1,2,4], Doctor Antoine Dupuis[1,2,3], Doctor Sami Haddad[4], Doctor Nicolas Venisse[1,2,3]

[1]EATHER Research Group, Inserm CIC 1402, University Hospital of Poitiers, Poitiers, France, [2]IHES Research Group, UMR CNRS 7267 EBI Laboratory, University of Poitiers, Poitiers, France, [3]Biology-Pharmacy-Public Health Department, University Hospital of Poitiers, Poitiers, France, [4]Department of Environmental and Occupational Health, School of Public Health, CReSP, Université de Montréal, Montreal, Canada

234 Log P and Log D are good descriptors for assessing the choice between standard, gel or mechanical separator tubes for therapeutic drug monitoring/toxicology screening procedures.

Mme Ekaterina Iakovleva[1], Dr Aurelien Schrapp[2], Dr Fabien Lamoureux[2,3], Dr Emmanuel Bourgogne[1,4]

[1]laboratoire de pharmacologie/toxicologie, hopital Bichat, AP-HP, Paris, France, [2]laboratoire de pharmacologie/toxicologie et pharmacogénétique, CHU Rouen, Rouen, France, [3]Inserm U1096, Université de Normandie, UNIROUEN, Rouen, France, [4]laboratoire de toxicologie, Pharmacie, Faculté de Santé, Université Paris Cité, Paris, France

235 Different drug annotation strategies in molecular networking approach on a panel of 60 patients : CFM-ID vs MetGem tools

Mr Sacha Guilhaumou[1], Dr Romain Magny[2,3], Dr Emmanuel Bourgogne[1,4]

[1]Laboratoire de toxicologie, Faculté de Santé, Pharmacie, Université Paris Cité, Paris, France, [2]Laboratoire de Toxicologie, Fédération de Toxicologie, Hôpital Lariboisière, AP-HP, Paris, France, [3]CiTCoM, CNRS, Université Paris Cité, Paris, France, [4]Laboratoire de Pharmacologie, hôpital Bichat, AP-HP, Paris, France

236 CFM-ID : a tool for building drug databases AND increasing the drug annotation in clinical toxicology using High Resolution Mass Spectrometry and Molecular Network

M Sacha Guilhaumou[1], Dr Romain Magny[2,3], Dr Emmanuel Bourgogne[1,4]

[1]Laboratoire de Toxicologie, Faculté de Santé, Pharmacie, Université Paris Cité, Paris, France, [2]Laboratoire de Toxicologie, Fédération de Toxicologie, Hôpital Lariboisière, AP-HP , Paris, France, [3]CiTCoM, CNRS, Université Paris Cité, Paris, France, [4]Laboratoire de Pharmacologie, hôpital Bichat, AP-HP, Paris, France

237 Valproic acid intoxication: A case report of a pediatric case

Dr Maleke Sassi[1,2], Dr Sana Boujaafar[1,2,3], Dr Dorra Amor[1,2,3], Dr Dalèl Nasralli[4], Dr Fadwa Majdoub[4], Dr Refka Hassine[1,2,3], Dr Asma Benabdelaziz[1,2,3], Pr Nabila Ben Rejeb[1,2,3], Pr Asma Omezzine[1,2,3], Pr Jalel Chemli[4], Pr Ali Bouselama[1,2,3]

[1]Departement of biochemistry Hospital University Sahloul, Sousse, Tunisia, [2]Faculty of Pharmacy of Monastir , Monastir , tunisia , [3]University of Monastir , Monastir , Tunisia , [4]Departement of pediatrics Hospital university Sahloul, Sousse , Tunisia

238 Phosphatidylethanol as a biological marker for alcohol consumption: Results from 24 574 subjects included in the HUNT4 Study

Phd Ragnhild Bergene Skråstad[1,2], Trond Oskar Aamo[1], Trine Naalsund Andreassen[1], Hilde Havnen[1], Kristian Hveem[3,4], Steinar Krokstad[4], Øyvind Salvesen[5], Olav Spigset[1,2]

[1]Department Of Clinical Pharmacology, St. Olav University Hospital , Trondheim, Norge, [2]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norge, [3]K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, Faculty of Medicine and Health Science, Norwegian University of Science and Technology, Trondheim, Norge, [4]HUNT Research Centre, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Levanger, Norge, [5]Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norge

239 Presence of a cocktail of endocrine disruptors in the breast adipose tissue of women with and without cancerous lesions.

PhD student Luyao Wu[1], Julien Robin[1,2,3], Doctor Marion Albouy[1,2,3], Doctor Cédric Nadeau[4], Doctor Virginie Migeot[5], Doctor Antoine Dupuis[1,2,3], Dcotor Guillaume Binson[1,2,3], Doctor Nicolas Venisse[1,2,3]
[1]IHES Research Group, UMR CNRS 7267 EBI Laboratory, University of Poitiers, Poitiers, France, [2]EATHER Research Group, Inserm CIC 1402, University Hospital of Poitiers, Poitiers, France, [3]Biology-Pharmacy-Public Health Department, University Hospital of Poitiers, Poitiers, France, [4]Obstetrics and Gynaecology Department, University Hospital of Poitiers, Poitiers, France, [5]Public Health Department, University Hospital of Rennes, Rennes, France

240 Delayed Neurological Sequelae after Accidental CO-intoxication or Post Traumatic Stress from a Near-Death Experience?

MD, PhD Ingebjørg Gustavsen[1], MD, PhD Einar August Høgestøl, MD,PhD Fridtjof Heyerdahl
[1]Department of Pharmacology, Oslo University Hospital, , Norway

241 Therapeutic drug monitoring for levetiracetam in pediatric patients with epilepsy: pharmacokinetics and therapeutic concertation range

Mr Yoshiaki Yamamoto[1], Ms. Akiko Ohta[1], Dr Naotaka Usui[1], Dr Katsumi Imai[1], Dr Yoshiyuki Kagawa[2], Dr Yukitoshi Takahashi[1]
[1]National Epilepsy Center, NHO, Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan, [2]Graduate School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, Japan

243 Assessment of pentaerythrityl tetranitrate-metabolites in pregnant woman and sheep and elucidation of their placental transfer – Application of a validated liquid chromatographic mass spectrometric approach

Dr. Daniela Wissenbach[1], Dr. Silke Große[2], Prof. Tanja Groten[2], PD Dr. Frank T. Peters[1]
[1]Jena University Hospital, Institute for Forensic Medicine, Am Klinikum 1, Friedrich Schiller University Jena, Germany, Jena, Germany, [2]Jena University Hospital, Placenta Lab, Department of Obstetrics, Am Klinikum 1, Friedrich Schiller University Jena, Germany, Jena, Germany

244 Early tacrolimus exposure is associated with BK-viremia in kidney transplant recipients

M.d. Soufian Meziyerh[1,2], Aline L. van Rijn[3], Danny van der Helm[2], Paul J.M. van der Boog[1,2], Teun van Gelder[4], Aloysius C.M. Kroes[3], Johan W. de Fijter[1,2], Dirk Jan A.R. Moes[4], Joris I. Rotmans[1,2], Mariet C.W. Feltkamp[3], Aiko P.J. de Vries[1,2]
[1]Deprt. of Medicine, Div. of Nephrology, Leiden University Medical Center, 2333 ZA, Leiden, The Netherlands., Leiden, Netherlands, [2]LUMC Transplant Center, Leiden, Netherlands, [3]Deprt. of Medical Microbiology, Leiden University Medical Center, 2333 ZA, Leiden, The Netherlands., Leiden, Netherlands, [4]Deprt. of Clinical Pharmacy and Toxicology, Leiden University Medical Center, 2333 ZA, Leiden, The Netherlands., ,

245 Impact of incomplete clinical information on antibiotic's therapeutic drug monitoring interpretation

Dr Maeva Palayer[1], Dr Laurent Massias[1], Dr Emmanuel Bourgogne[1]
[1]laboratoire de pharmacologie, hôpital Bichat, AP-HP, Paris, France, [2]laboratoire de toxicologie, Faculté de Santé-Pharmacie, Université Paris Cité, Paris, France

246 Mycophenolic Acid Exposure Determines Antibody Formation Following SARS-CoV-2 Vaccination in Kidney Transplant Recipients: A Nested Cohort Study

M.d. Soufian Meziyerh[1,2], Pim Bouwmans[3,4], Teun van Gelder[5], Danny van der Helm[2], Lianne Messchendorp[6], Paul van der Boog[1,2], Johan de Fijter[1,2], Dirk Jan Moes[4], Aiko de Vries[1,2]
[1]Department of Medicine, Division of Nephrology, Leiden University Medical Center, Leiden, The Netherlands., , Netherlands, [2]Leiden University Medical Center Transplant Center, Leiden University

Medical Center, Leiden, The Netherlands., , , [3]Department of Internal Medicine, Division of Nephrology, Maastricht University Medical Center, Maastricht, The Netherlands., , , [4]Cardiovascular Research Institute Maastricht School for Cardiovascular Disease, University of Maastricht, Maastricht, The Netherlands., , , [5]Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands., , , [6]Department of Nephrology, University Medical Center Groningen, Groningen, The Netherlands., ,

247 Population Pharmacokinetics, Pharmacogenomics, and Adverse Events of Osimertinib and its Two Active Metabolites, AZ5104 and AZ7550, in Japanese Patients with Advanced Non-small Cell Lung Cancer: A Prospective Observational Study

Dr. Emi Ishikawa[1], Senior Asst. Prof. Yuta Yokoyama[1,2], Ms. Chishima Haruna[2], Assoc. Prof. Kasai Hidefumi[3], Mr. Ouki Kuniyoshi[4], Mr. Kimura Motonori[5], Dr. Jun Hakamata[5], Mr. Hideo Nakada[5], Mr. Naoya Suehiro[5], Dr. Naoki Nakaya[6], Dr. Hideo Nakajima[6], Senior Asst. Prof. Shinnosuke Ikemura[7], Assoc. Prof. Hiroyuki Yasuda[8], Assoc. Prof. Ichiro Kawada[8,9], Senior Asst. Prof. Hideki Terai[8,10], Asst. Prof. Aya Jibiki[2], Assoc. Prof. Hitoshi Kawazoe[1,2], Professor Kenzo Soejima[7], Gen. Hiroshi Muramatsu[5], Professor Sayo Suzuki[1,2], Professor Tomonori Nakamura[1,2]

[1]Division of Pharmaceutical Care Sciences, Keio University Graduate School of Pharmaceutical Sciences, Minato-ku, Japan, [2]Division of Pharmaceutical Care Sciences, Center for Social Pharmacy and Pharmaceutical Care Sciences, Keio University Faculty of Pharmacy, Minato-ku, Japan, [3]Laboratory of Pharmacometrics and Systems Pharmacology, Keio Frontier Research and Education Collaboration Square (K-FRECS) at Tonomachi, Keio University, Kawasaki-shi, Japan, [4]Department of Pharmacy, Ageo Central General Hospital, Ageo-shi, Japan, [5]Department of Pharmacy, Keio University Hospital, Shinjuku-ku, Japan, [6]Department of Oncology, Ageo Central General Hospital, Ageo-shi, Japan, [7]Department of Respiratory Medicine, Graduate School of Medicine, University of Yamanashi, Chuo-shi, Japan, [8]Division of Pulmonary Medicine, Department of Medicine, Keio University School of Medicine, Shinjuku-ku, Japan, [9]Health Center, Keio University, Yokohama-shi, Japan, [10]Keio Cancer Center, School of Medicine, Keio University School of Medicine, Shinjuku-ku, Japan

248 Development and Validation of an HPLC-UV method for Determination of Ceftobiprole in human serum

PhD Valeria Marini[1,2], Medical Resident in Clinical Pharmacology and Toxicology Fabio Sacco[1,2], Medical Resident in Clinical Pharmacology and Toxicology Michela Caviglia[1,2], Fabio Piras[1,2], Medical Resident in Clinical Pharmacology and Toxicology Fabio Piras[1,2], Doctor of Medicine Silvia Boni[3], Director Emanuele Pontali[3], Professor Francesca Mattioli[1,2]

[1]Department of Internal Medicine- University of Genoa , Genoa, Italy, [2]Clinical Pharmacology Unit , Galliera Hospital, Genoa, Italy, [3]Department of Infectious Diseases, Galliera Hospital, Genoa, Italy

249 Quantification of tacrolimus in scalp hair of lung and kidney transplant recipients

Ms Tanja Zijp[1], Ms Lenneke Junier[1], dr. Job Van Boven[1], dr. Tji Gan[1], prof.dr. Stephan Bakker[1], prof.dr. Daan Touw[1]

[1]UMCG, Groningen, Netherlands

250 Population pharmacokinetic modeling of CSF to blood clearance

Markus Hovd[1], Espen Mariussen[2,3], Hilde Uggerud[2], Aslan Lashkarivand[4], Hege Christensen[1], Geir Ringstad[5], PK Eide[3]

[1]Section for Pharmacology and Pharmaceutical Biosciences, Department of Pharmacy, University of Oslo, , Norway, [2]Norwegian Institute for Air Research, , Norway, [3]Department of Air Quality and Noise, Norwegian Institute of Public Health, , Norway, [4]Department of Neurosurgery, Oslo University Hospital, , Norway, [5]Division of Radiology and Nuclear Medicine, Department of Radiology, Oslo University Hospital, , Norway

252 Use of vancomycin population pharmacokinetic model in pediatric patients with cystic fibrosis: impact of data on the predictive performance

Aysenur Yaliniz[1,2], Mathieu Blouin[1,2], Marie-Élaine Métras[2,3], Camille Gaudreault[4,5], Marie Christine Boulanger[4,5], Karine Cloutier[4,5], Marie-Hélène Dubé[4,5], Isabelle Viel-Thériault[5], Julie Autmizguine[6,7,8], Amélie Marsot[1,2,8]

[1]Laboratoire STP2, Faculté de Pharmacie, Université de Montréal, Montréal, Canada, , , [2]Faculté de Pharmacie, Université de Montréal, Montréal, Canada, , , [3]Département de Pharmacie, Centre Hospitalier Universitaire Sainte Justine, Montréal, Canada, , , [4]Faculté de Pharmacie, Université Laval,

Québec, Canada, , , [5]Département de Pharmacie, Centre Hospitalier Universitaire de Québec-Université Laval, Québec, Canada, , , [6]Département de Pharmacologie, Faculté de Médecine, Université de Montréal, Montréal, Canada, , , [7]Unité de Pharmacologie Clinique, Centre Hospitalier Universitaire Sainte Justine, Montréal, Canada, , , [8]Centre de recherche, Centre Hospitalier Universitaire Sainte Justine, Montréal, Canada, ,

254 Development of the My-5FU immunoassay on the IDS-ISYS automate for therapeutic drug monitoring of 5-Fluorouracile

Benedicte Franck[1], Marie-José Ferrand-Sorre[1], Jodi Courtney[2], Florian Lemaitre[1], Marie-Clémence Verdier[1], Dr Camille Tron[1]

[1]Pharmacology department, University of Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) – UMR_S 1085, Rennes, France, [2]Saladax Biomedical, Inc., Bethlehem,

255 Frequency of the CYP2C19*2 and CYP2C19*17 polymorphism in an Argentinian pediatric cohort and its effect on voriconazole plasma concentration.

Dr. Santiago Zugbi[1], Dra Verónica Araoz[1], Pharm. Juliana Testard[1], Bs. Milagros Dinardi[1], Bs. Christian Olivetti[1], Pharm. Lucas Brstilo[1], Dra. Adriana Sassone[1], Med. Fernanda Conde[1], Med. María Victoria Ponce[1], Med. Analía Julia[1], Dra. Cristina Alonso[1], Dra. Natalia Riva[3], Dra. Paula Schaiquevich[1,2], Paula Schaiquevich

[1]Hospital De Pediatría Garrahan, Buenos Aires, Argentina, [2]National Scientific and Technical Council, Buenos Aires, Argentina , [3]School of Pharmacy and Nutrition, University of Navarra, Pamplona, Spain

259 Oxycodone, morphine, and fentanyl in patients with chronic pain: Proposal of dose-specific concentration ranges

MD, PhD Cecilie Hasselø Thaulow[1], MD, PhD Arne Helland[2,3], MD, PhD Ulf Erik Kongsgaard[4,5], MD, PhD Gudrun Høiseth[1,5,6]

[1]Department of Forensic Sciences, Division of Laboratory Medicine, Oslo University Hospital, Oslo, Norway, [2]Department of Clinical Pharmacology, St. Olav University Hospital, Trondheim, Norway, [3]Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway, [4]Department of Anesthesiology, Division of Emergencies and Critical Care, Oslo University Hospital,, Oslo, Norway, [5]Institute of Clinical Medicine, Medical Faculty, University of Oslo, Oslo, Norway, [6]Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway

260 Development of an LC-MS/MS method for the simultaneous determination of four antiepileptic drugs in dried plasma spots – Comparison of plasma generated by membrane filtration and by centrifugation

Biomedical laboratory Science Julia Mahunu Ngudie[1], PhD Michael Tekle[1], PhD Camilla Linder[1], Phd Victoria Barclay[1]

[1]Medical Unit for Clinical Pharmacology, Karolinska University Hospital, Sweden, Huddinge, Sverige

261 Development of a method for the quantification of fluoroquinolones and antiviral drugs using volumetric absorptive microsampling.

Dr Bénédicte Franck[1], Mrs Marie-José Ferrand-Sorre[1], Dr Camille Tron[1], Dr Marie-Clémence Verdier[1], Dr Florian Lemaitre[1]

[1]University of Rennes, Centre Hospitalier Universitaire Rennes, École des Hautes Études en Santé Publique, IRSET (Institut de Recherche en Santé, Environnement et Travail), UMR S 1085, Rennes, France. , Rennes, France

262 Prevalence of Pharmacogenomic variables of Tacrolimus in patients of Renal Transplantation and their significance in Dose Requirement

Dr Smita Pattanaik[1], Ms Priyanka Naithani[1], Dr Deepesh Kenwar[1], Dr Savita Verma Atri[1], Mr Ajay Patial[1], Mr Sumit Dey[1], Ms Ritika Panwar[1], Ms Sheetal Singh[1], Dr Karthik V[1], Dr Shiva Kumar Patil[1], Dr Sarbpreet Singh[1], Dr Ashish Sharma[1]

[1]Post Graduate Institute of Medical Education And Research Chandigarh, Chandigarh, India

263 Detection of phosphatidylethanol in units of banked blood and its potential impact to interpretation of alcohol use.

Dr. Carmen Gherasim[1]

[1]University Of Michigan, Ann Arbor, United States

264 A novel method to quantify the microbiome-derived metabolism of mycophenolic acid in human fecal samples.
Master Of Science Ole Martin Drevland[1], PhD Eric J. de Muinck[3], PhD Anders Åsberg[1,2], MD, PhD Karsten Midtvedt[2], PhD Ida Robertsen[1]
[1]Department of Pharmacy, University Of Oslo, , Norway, [2]Department of Transplantation Medicine, Oslo University Hospital, , Norway, [3]Centre for Ecological and Evolutionary Synthesis, Department of Biosciences, University of Oslo,, , Norway
265 The impact of immunological risk and tacrolimus variability on allograft rejection in pediatric liver transplantation
Guido Trezeguet Renatti[1,2], Julia Minetto[1], Agostina Arrigone[1], Cintia Yanina Marcos[1], Gabriela Aboud[1], Hayellen Reijenstein[1], Leandro Lauferman[1], Maria Florencia D'Arelli[1], Agustina Jacobo Dillon[1], Diego Aredes[1], Daniela Fernandez Souto[1], Gustavo Wildfeuer[1], Cecilia Gamba[1], Marcelo Dip[1], Oscar Imventarza[1], Esteban Halac[1], Paula Schaiquevich[1,2]
[1]Hospital Garrahan, , Argentina, [2]CONICET, , Argentina
266 Isobaric interferences by drug metabolites in liquid chromatography-tandem mass spectrometric methods (LC-MS/MS): A case with a pipamperone metabolite
PhD Christoph Schöberl[1], Sina Junger[1], Nicole Erlacher[2], Alexandra Voss[1], Kevin Wanek[1], Dr. med. Eberhard Wieland[1], Maria Shipkova[1]
[1]Competence Center for Therapeutic Drug Monitoring, MVZ Leinfelden-Echterdingen GmbH, Synlab Holding Germany GmbH, Leinfelden-Echterdingen, Germany, [2]Vitos Clinic for Forensic Psychiatry Haina, Vitos GmbH, Haina, Germany
267 Comparison of LC-MS and a Benzodiazepine Immunoassay in Urine Samples to Assess Compliance in Poly Drug Abusers Undergoing a Detoxification Program with Oxazepam.
Prof. Dr. Eberhard Wieland[1], Sonja Martin[1], PD Dr. Maria Shipkova[1]
[1]Synlab Medical Center Leinfelden-Echterdingen, Leinfelden-Echterdingen, Germany
270 Blood ammonia level was rarely correlated to the serum valproate concentration: a retrospective analysis of real-world data
MD Jiyeon Park[1], MD Ki Young Huh[1], MD, PhD SeungHwan Lee[1], MD, PhD Jae Yong Chung[2], MD, PhD In Jin Jang[1], MD, PhD Jae Seong Oh[1]
[1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, , South Korea, [2]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Bundang Hospital, Seongnam, , South Korea
271 Clinical Implementation of DPYD Genotyping Test for Guiding Fluoropyrimidine Therapy
Dr. Lei Fu[1,2], Betty Wong[1], Michael Jonathon Raphael[1,2], Carlo De Angelis[1,2], Weei-Yuarn Huang[1,2], David Hwang[1,2]
[1]Sunnybrook Health Sciences Centre, Toronto, Canada, [2]University of Toronto, Toronto, Canada
273 A Retrospective Quality Review of Vancomycin Target Attainment in a Haematology Ward at a University Hospital in Sweden
Pharmacist Emelie Lefvert[1], Pharmacist Maria Swartling[2], PhD Anna-Karin Hamberg[2,3], PhD Elisabeth Nielsen[2]
[1]Uppsala University Hospital, UPPSALA, Sverige, [2]Department of Pharmacy, Uppsala University, UPPSALA, Sverige, [3]Division of Clinical Pharmacology, Uppsala University Hospital, UPPSALA, Sverige
274 Optimal sample times for monitoring quetiapine extended release.
Azucena Aldaz[1], PhD Maria del Mar Unceta[1], Pharm D Carmen Barace, PhD Patricio Molero
[1]Clínica Universidad De Navarra, Pamplona, Spain
275 Finger-prick sampling for the monitoring of tacrolimus, creatinine and hemoglobin in kidney transplant recipients: Assessment of self-sampling and healthcare professional-performed sampling with two volumetric devices
MScPharm, PhD Nils Tore Vethe[1], MScPharm, PhD Anders Åsberg[5], BSc Anders M. Andersen[1], MD, PhD Ragnhild Heier Skauby[3], MScPharm, PhD Stein Bergan[4], MD, PhD Karsten Midtvedt[2]
[1]Department of Pharmacology, Oslo University Hospital, Oslo, Norway, [2]Department of Transplantation Medicine, Oslo University Hospital, Oslo, Norway, [3]Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway, [4]Department of Pharmacology, Oslo University Hospital and Department of Pharmacy, University of Oslo, Oslo, Norway, [5]Department of

Transplantation Medicine, Oslo University Hospital and Department of Pharmacy, University of Oslo, Oslo, Norway

276 Pharmacogenomics of tramadol in Japanese orthopedic surgery patients

Dr Tomohiro Terada[1], Dr Takaki Kamiya[2], Dr Daiki Hira[1], Dr Ryo Nakajima[3], Ms Kazuha Shinoda[4], Ms Atsuko Motomochi[2], Ms Aya Morikouchi[2], Dr Yoshito Ikeda[2], Dr Tetsuichiro Isono[2], Mr Michiya Akabane[2], Dr Satoshi Ueshima[4], Dr Shinji Imai[3], Dr Mikio Kakumoto[4]

[1]Department of Clinical Pharmacology and Therapeutics, Kyoto University Hospital, Kyoto, Japan, [2]Department of Pharmacy, Shiga University of Medical Science Hospital, Otsu, Japan, [3]Department of Orthopaedic Surgery, Shiga University of Medical Science, Otsu, Japan, [4]College of Pharmaceutical Sciences, Ritsumeikan University, Kusatsu, Japan

277 Adalimumab serum levels and anti-drug antibodies: associations to treatment response and drug survival in inflammatory arthritis patients

Md, Phd Student Ingrid Jyssum[1,2], MD, PhD Johanna Elin Gehin[3], PhD Joseph Sexton[1], MD, PhD Eirik K Kristianslund[1], MD, PhD Yi Hu[4], PhD David J Warren[3], MD, PhD, Professor Tore K Kvien[1,2], MD, PhD, Professor Espen A Haavardsholm[1,2], MD, PhD Silje Watterdal Syversen[1], MD, PhD Nils Bolstad[3], MD, PhD Guro Løvik Goll[1]

[1]Center for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, Oslo, Norway, [2]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway, [3]Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway, [4]Lillehammer Hospital for Rheumatic Diseases, Lillehammer, Norway

278 A comparative analysis of therapeutic drug monitoring (TDM) implementation in Greece in the last 20 years

Prof Vangelis Manolopoulos[1,2], Ms Gavriela Voulgaridou[1], Ms Theodora Paraskeva[1], Ms Natalia Atzemian[1], Konstantina Portokallidou[1,2], Dr Georgia Ragia[1], Prof George Kolios[1,2], Dr Konstantinos Arvanitidis[1,2]

[1]Laboratory of Pharmacology, Individualized Medicine and Pharmacological Research Solutions (IMPReS) Center,Democritus University of Thrace Medical School, Alexandroupolis, Greece, [2]Clinical Pharmacology Unit, Academic General Hospital of Alexandroupolis, Alexandroupolis, Greece

279 In vivo protein binding investigation of first-line antituberculosis drugs

Mr David Fage[1], Prof. Frédéric Cotton[1]

[1]Laboratoire Hospitalier Universitaire De Bruxelles – Universitair Laboratorium Brussel (LHUB-ULB), Brussels, Belgium

280 In vitro protein binding investigation of second-line antituberculosis drugs

Mr David Fage[1], Prof. Frédéric Cotton[1]

[1]Laboratoire Hospitalier Universitaire De Bruxelles – Universitair Laboratorium Brussel (LHUB-ULB), Brussels, Belgium

281 Performance Evaluation of an Automated Assay for Measurement of Everolimus* on the Atellica® Solution Immunoassay Analyzer

Dr Sarah Baxter[1], Mr Nigel Casson[1], Mrs Clare Murray[1], Ms Louise Hanson[1], Mr Tom Chuang[2]

[1]Randox Laboratories Ltd., Crumlin, United Kingdom, [2]Siemens Healtineers, Tarrytown, United States of America

282 Performance Evaluation of an Automated Assay for Measurement of Tacrolimus* on the Atellica® Solution Immunoassay Analyzer

Dr Sarah Baxter[1], Mr Ross Swan[1], Ms Oliwia Sankiewicz[1], Mr Nigel Casson[1], Mr Tom Chuang[2]

[1]Randox Laboratories Ltd., Crumlin, United Kingdom, [2]Siemens Healthineers, Tarrytown, United States of America

283 Performance Evaluation of an Automated Assay for Measurement of Sirolimus* on the Atellica® Solution Immunoassay Analyzer

Dr Sarah Baxter[1], Mr Nigel Casson[1], Mrs Clare Murray[1], Ms Louise Hanson[1], Mr Tom Chuang[1]

[1]Randox Laboratories Ltd., Crumlin, United Kingdom, [2]Siemens Healthineers, Tarrytown, United States of America

284 Ultra-fast, Accurate and Simultaneous Quantification of Ritonavir and Lopinavir in Human Plasma

Mr Aymeric Morla[1], Mr Mats Garmer[1], Mr Rahul Baghla, Mr Rolf Kern

[1]Sciex, , France

285 Model-informed infliximab dosing and clearance monitoring of a patient with acute severe ulcerative colitis

Dr. Zhigang Wang[1], Dr. Wannee Kantasirpitak[1], Dr. Debby Thomas[1], Dr. Prof. João Sabino[2,3], Dr. Prof. Marc Ferrante[2,3], Dr. Prof. Bram Verstockt[2,3], Dr. Prof. Séverine Vermeire[2,3], Dr. Prof. Erwin Dreesen[1]

[1]University of Leuven, Department of Pharmaceutical and Pharmacological Sciences, Leuven, Belgium, [2]University of Leuven, Department of Chronic Diseases and Metabolism, Leuven, Belgium, [3]University Hospitals Leuven, Department of Gastroenterology and Hepatology, Leuven, Belgium

286 Infliximab clearance predicts the risk of relapse during maintenance treatment of patients with inflammatory bowel disease

Dr. Zhigang Wang[1], Dr. Prof. Niels Vande Casteele[2], Dr. Prof. Marc Ferrante[3,4], Dr. Prof. Séverine Vermeire[3,4], Dr. Prof. Erwin Dreesen[1]

[1]Department of Pharmaceutical and Pharmacological Sciences, University of Leuven, Leuven, Belgium, [2]Department of Medicine, University of California San Diego, San Diego, Belgium, [3]Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium, [4]Department of Chronic Diseases and Metabolism, University of Leuven, Leuven, Belgium

287 Correlation between AUC of Mycophenolate Mofetil and its gastrointestinal tolerability in renal transplant recipients

Ms Priyanka Naithani[1], Dr. Smita Pattanaik[1], Dr. Ashish Sharma[2], Ms. Ritika Panwar[1], Ms. Sheetal Singh[1], Mr. Sumit Dey[3], Ms. Neeru Sharma[1], Dr. Shiva Patil[2], Dr. Sarabpreet Singh[2], Dr. Deepesh B. Kenwar[2]

[1]Department of Pharmacology, Postgraduate Institute Of Medical Education And Research, Chandigarh, chandigarh, India, [2]Department of Renal Transplant Surgery, Postgraduate institute of medical education and research, Chandigarh, Chandigarh, India, [3]Department of Urology, Postgraduate institute of medical education and research, Chandigarh, Chandigarh, India

288 Role of uracil and dihydrouracil (DHU) to predict serious adverse events with 5-Fluorouracil in patients with malignancy

Dr Binu Susan Mathew[1], Dr Ajoy Oommen John[1], Dr Poornima Sivamani[1], Dr Ashish Singh[1], Dr Sumith K Mathew[1], Dr Gowri Mahasampath[1], Dr Anjana Joel[1], Dr Ratna Prabha[1], Dr Raju Titus Chacko[1]

[1]Christian Medical College Vellore, Vellore, India

289 TDM of antiseizure medication through quantitative DBS

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[1]IRCCS Istituto delle Scienze Neurologiche di Bologna, Full Member of the European Reference Network for Rare and Complex Epilepsies (EpiCARE), Bologna, Italy, Italy, [2]Department of Chemistry "G. Ciamician", University of Bologna, Bologna, Italy, Italy

290 Vincristine pharmacokinetics in patients with malignant lymphoma

MD, PhD Ragnhild Heier Skauby[1], BSc Anders Mikal Andersen[2], MSc, Pharm, PhD Nils Tore Vethe[2], MSc, Pharm, PhD Stein Bergan[2,3]

[1]Department of Medical Biochemistry, Oslo University Hospital , Oslo, Norway, [2]Department of Pharmacology, Oslo University Hospital, Oslo, Norway, [3]Department of Pharmacy, the University of Oslo, Norway, Oslo, Norway

291 Atorvastatin lactonization is associated with statin-dependent muscular side effects in patients with coronary heart disease

Md, Phd Candidate Trine Lauritzen[1,2], Professor John Munkhaugen[1,2], PhD Kari Peersen[4], PhD Oscar Kristiansen[1], PhD Elise Sverre[3], Anders M Andersen[3], Professor Stein Bergan[3,4], MD, PhD Einar Huseby[1], PhD Nils Tore Vethe[3]

[1]Vestre Viken Hospital Trust, Drammen, Norway, [2]University of Oslo, Oslo, Norway, [3]Oslo University Hospital, , Norway, [4]Vestfold Hospital Trust, , Norway

292 The role of pharmacogenetics as a possible risk factor for dabigatran–associated bleeding

Jozefina Palić[1], Assistant professor Lana Ganoci[2], PhD Livija Šimičević[2], Assistant professor, MD Majda Vrkić Kirhmajer[3], MD Hrvoje Holik[4], Student Ivana Prpić[5], Assistant professor Tamara Božina[1]

[1]Department of Medical Chemistry, Biochemistry and Clinical Chemistry, University of Zagreb, School of Medicine, Zagreb, Croatia, [2]Division of Pharmacogenomics and Therapy Individualization, Department of Laboratory Diagnostics, University Hospital Centre Zagreb, Zagreb, Croatia, [3]Department of Cardiology, University Hospital Centre Zagreb, University of Zagreb, School of Medicine, Zagreb, Croatia, [4]Department of Internal Medicine, "Dr. Josip Benčević" General Hospital, Slavonski Brod, Croatia, [5]Faculty of Pharmacy and Medical Biochemistry, University of Zagreb, Zagreb, Croatia

293 Distinguishing multimer from dimer antidrug antibody complexes with infliximab or adalimumab using HMSA is relevant to drug dosing decisions

Ms Paula Keating[1], Dr John O'Donnell[1], Professor Murray Barclay[2]
[1]Canterbury Health Laboratory, Te Whatu Ora-Health New Zealand, Christchurch, New Zealand, [2]Christchurch Hospital, Te Whatu Ora-Health New Zealand, Christchurch, New Zealand

299 Cefotaxime dosing strategy and target concentrations should be reconsidered in critically-ill patients

Théo Dillie[1], Pr Guillaume Thiery[1], Pr Jérôme Morel[1], Dr Rémi Balluet[1], Dr Manon Launay[1], Dr Sophie Perinel-Ragey[1]
[1]Chu Saint Etienne, Saint Etienne, France

300 The association between reached therapeutic range of valproic acid and seizure control in Thai pediatric epilepsy patients

Dr. Suthida Boonsom[1,2], Chutikan Sriprom[1], Phatcharin Sinthao[1], Pennipa Sukhpimai[1]
[1]Department of Pharmaceutical Care, School of Pharmaceutical Sciences, University of Phayao, Muang, Thailand, [2]Unit of Excellence on Pharmacogenomic Pharmacokinetic and Pharmacotherapeutic Research (UPPER), School of Pharmaceutical Sciences, University of Phayao, Muang, Thailand

301 Detection and quantitation of protonitazene in a case of acute respiratory arrest

Mr Jon Andsnes Berg[1], Mr Marcus Stangeland[1], Mr Torbjørn Lunde[1], Mr Kjell Ove Fossan[1]
[1]Haukeland University Hospital, , Norway

302 Impact of age and sex on the exposure of six antipsychotics, based on routine therapeutic drug monitoring (TDM) data from 20 000 patients

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303 Ultrarapid metabolism of non-clozapine antipsychotics preceding switch to clozapine treatment

Hasan Çağın Lenk[1,2], Robert Løvsletten Smith[1], Espen Molden[1,2]
[1]Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway, [2]Section for Pharmacology and Pharmaceutical Biosciences, Department of Pharmacy, University of Oslo, Oslo, Norway

Safety profile of drug-drug interaction between amenamevir with calcineurin inhibitors: case reports

Mr. Toshinori Hirai[1], Dr. Tomohiro Murata[2], Dr. Akihiro Tanemura[3], Prof. Shugo Mizuno[3], Prof. Takuya Iwamoto[1]
[1]Department of Pharmacy, Tsu, Japan, [2]Department of Nephrology, Tsu, Japan, [3]Department of Hepatobiliary Pancreatic and Transplant Surgery, Tsu, Japan

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction

Amenamevir binds to helicase-primer, thereby inhibiting DNA replication in herpes simplex virus and varicella-zoster virus. Landmark trials demonstrate that oral administration of amenamevir 400 mg ×1 for 7 days is non-inferior to valacyclovir in the risk-benefit profile. In vitro study identified that amenamevir concentration clinically activates a major drug-metabolizing enzyme, cytochrome P450 3A4 (CYP3A4) by approximately 30% (vs. rifampin). A clinical pharmacokinetic study also indicated that amenamevir decreases the area under the blood concentration-time curve of midazolam (a typical CYP3A4 substrate) by approximately 50%. However, it remains unclear whether amenamevir influences the pharmacokinetics and clinical effects of calcineurin inhibitors (tacrolimus and cyclosporine) metabolized by CYP3A4/5. We show safety profiles of drug-drug interaction with amenamevir and calcineurin inhibitors.

Materials and Methods

We recruited 2 subjects who co-administered amenamevir and calcineurin inhibitors at Mie University Hospital and obtained written informed consent from them. The concentration/dose normalized by body weight was an index of exposure to calcineurin inhibitors.

Results

A 63-year-old female (61.6 kg) undertook sustained-release tacrolimus (Graceptor Capsules, Astellas Pharma Inc.) 1.0 mg ×1 after living-donor liver transplantation due to hepatocellular carcinoma. Genotypes of CYP3A5 were CYP3A5*3/*3 in both the recipient and donor. When the recipient was diagnosed with varicella-zoster virus, she temporarily withdrew tacrolimus from days 1 to 2. Thereafter, the same dosage of tacrolimus was restarted from day 3. There was no significant difference in the C/D ratio before and after concomitant use of amenamevir 400 mg ×1 for 4 days (day -16: 4.5 ng/mL, 277.2 ng/mL/mg/kg vs. day 5: 3.6 ng/mL, 221.8 ng/mL/mg/kg). She did not develop severe adverse outcomes such as graft rejection.

A 71-year-old female (52.5 kg) undertook microemulsion cyclosporine (Neoral Capsules, Novartis Pharma Co.) 50 mg ×2 as induction therapy for nephrotic syndrome (membranous nephropathy). The genotype of CYP3A5 has not been tested. Blood cyclosporine concentrations at 2 hours post-dose were 153.5 ng/mL (80.6 ng/mL/mg/kg) on day 2 and 166.8 ng/mL (87.6 ng/mL/mg/kg) on day 4 when given amenamevir 400 mg ×1 for 5 days. After the end of amenamevir treatment, blood cyclosporine concentration at 2 hours post-dose on day 19 remained unchanged (170.4 ng/mL, 89.5 ng/mL/mg/kg). She achieved remission of nephrotic syndrome without any severe adverse outcomes.

Discussions and Conclusions

The present cases revealed that drug-drug interaction between amenamevir and calcineurin inhibitors was unnoticeable in low concentration ranges. Previous literature has shown the clinical significance of drug-drug interaction between CYP3A4 inducers and calcineurin inhibitors at high concentrations of calcineurin inhibitors. In the clinical pharmacokinetic study, the impact of amenamevir 400 mg ×1 for 10 days was examined, whereas our two cases received a short administration of amenamevir within 5 days.

In summary, concomitant use of amenamevir had little effect on the pharmacokinetics and clinical effects of calcineurin inhibitors of low concentration range. It may be important to consider both the exposure period of amenamevir and the therapeutic concentration of calcineurin inhibitors.

Expeditious quantification of plasma tacrolimus with liquid chromatography tandem mass spectrometry in solid organ transplantation

Ms Tanja Zijp[1], Mr Tim Knobbe[1], Mr Kai van Hateren[1], Jan Roggeveld[1], dr. Hans Blokzijl[1], dr. Tji Gan[1], prof.dr. Stephan Bakker[1], Erwin Jongedijk[1], X TransplantLines Investigators[1], prof.dr. Daan Touw[1]
[1]UMCG, Groningen, Netherlands

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Background: Traditionally, tacrolimus is assessed in whole blood samples, but this is suboptimal from the
perspective that erythrocyte-bound tacrolimus (>95%) is not a good representative of the active fraction (<1%). In this work, a straightforward and rapid method was developed for determination of plasma tacrolimus in solid organ transplant recipients.

Methods: A liquid chromatography tandem mass spectrometry (LC-MS/MS) method was developed Sample preparation was performed through protein precipitation of 200 µl plasma with a single dilution step with 500 µl methanol with stable isotopically labelled tacrolimus as internal standard. After, 20 µl was injected on the LC-MS/MS system. Separation was done using a chromatographic gradient on a C18 column (50 x 2.1 mm, 2.6 µm). Detection was performed using heated electrospray ionisation. Method validation was performed according to EMA and FDA guidelines, and samples from a clinical study were measured.

Results: The method was linear in the concentration range 0.05-5.00 µg/L, with within-run and between-run precision in the range 2-6% and a run time of 1.5 min. The method was validated for selectivity, sensitivity, carry-over, accuracy, and precision, process efficiency, recovery, matrix effect, and stability. A total of 2333 samples were measured from 1325 solid organ transplant recipients using tacrolimus (liver n=312, kidney n=1714, and lung n=307). The clinical samples had median plasma tacrolimus concentrations of 0.10 µg/L, 0.15 µg/L and 0.23 µg/L, respectively.

Conclusions: This method is suitable for measurement of tacrolimus in plasma and will facilitate ongoing observational and prospective studies on the relationship of plasma tacrolimus concentrations with
clinical outcomes.

Development, optimization, and validation of a simple isocratic HPLC-UV method for the simultaneous quantification of rifampicin and isoniazid in human plasma

Jawhar Rebai[1], PharmD Mohamed Hedi BEN CHEIKH[2], PharmD Haifa MASTOURI[1], Biological technician Ahlem SLAMA[1], MD Haifa BEN ROMDHANE[1], MD Amel CHAABENE[1], MD Zohra CHADLY[1], MD Najeh BEN FADHEL[1], MD Nadia BEN FREDJ[1], MD Karim AOUAM[1]
[1]Clinical Pharmacology Department, Fattouma Bourguiba Hospital Monastir, Tunisia, Monastir, Tunisia, [2]Laboratory LR12ES09 "Chemical, Galenic and Pharmacological Development of Drugs", Faculty of Pharmacy of Monastir, Tunisia, Monastir, Tunisia

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction
Tuberculosis remains a global public health problem. Its treatment is mainly based on the combination of antitubercular drugs, especially first-line drugs such as rifampicin (R) and isoniazid (I), which can cause numerous adverse effects. Hepatotoxicity remains the most frequent and the most dreaded, which can sometimes lead to therapeutic failure.
The development of a therapeutic drug monitoring technique for I and R remains necessary to prevent their adverse effects and and ensure treatment efficacy.

Materials and Methods
The HPLC system consisted of reversed-phase alkyl (C18) (250 mm×4.6 mm,5 µm) column, 0.02 mol•L-1 KH2PO4-acetonitrile-triethylamine (60:40:0.15,adjust pH to 4.30 with H3PO4) as mobile phase in isocratic mode, flow rate was 0.9 mL•min-1, column temperature was 25 °C with a UV lamp detection of isoniazid after derivation and rifampicin at 340 nm , the internal standard was clonazepam
Results
A satisfactory extraction after a simple deproteinisation yield was obtained, >60% for I and for R after plasma extraction optimization. The optimized chromatographic conditions were well validated with R2 = 0.9999 for I and R2 = 0.9997 for R, LOD = 0.3 µg/mL, LOQ = 1 µg/mL for I, and LOD = 0.5 µg/mL, LOQ = 1.5 µg/mL for R, the inter- and intra-day RSDs were lower than 15%. Rs analytes/internal standard >1.5
Discussions and conclusion
The validation results showed that our method is specific, sensitive and reproducible. To the best of our knowledge, this is the first HPLC-UV method with isocratic mode and requires only one deproteinization step prior to analysis, enabling simultaneous determination of rifampicin and isoniazid in human plasma with high sensitivity and specificity.
This method is presently simple and practical, and is ready for clinical application in the therapeutic drug monitoring of patients undergoing treatment with I and R

Serum concentrations of direct oral anticoagulants in patients admitted to hospital with a diagnosis of stroke

Dr Rachel Aakerøy[1,2], Dr Mari Nordbø Gynnild[3,4,5], Dr Lena Løfblad[6], Dr Roar Dyrkorn[1], Dr Hanne Ellekjær[3,7], Prof. Stian Lydersen[8], Dr Arne Helland[1,2], Prof. Olav Spigset[1,2]
[1]Department of Clinical Pharmacology, St Olavs University Hospital, Trondheim, Norway, [2]Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway, [3]Department of Stroke, Clinic of Medicine, St. Olavs University Hospital,, Trondheim, Norway, [4]Clinic of Cardiology, St. Olavs University Hospital, Trondheim, Norway, [5]Department of Circulation and Medical Imaging, Norwegian University of Science and Technology , Trondheim, Norway, [6]Department of Clinical Chemistry, St. Olavs University Hospital, Trondheim, Norway, [7]Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway, [8]Regional Centre for Child and Youth Mental Health and Child Welfare, Department of mental Health, Faculty of medicine and health Sciences, Norwegian University of Science and Technology, Trondheim, Norway

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction: No therapeutic ranges linking drug concentrations of direct oral anticoagulants (DOACs) to clinical outcomes have been defined. Nevertheless, low drug concentrations could be associated with therapeutic failure and a subsequent increased risk of stroke. We investigated whether serum concentrations of apixaban and rivaroxaban among patients admitted to hospital with a tentative diagnosis of stroke differed between those later verified to suffer from ischemic stroke or transient ischemic attack (TIA) and those having other diagnoses.

Materials and Methods: We included 102 patients admitted to St. Olav University Hospital, Trondheim, Norway, with a tentative diagnosis of stroke being treated with apixaban (84 %) or rivaroxaban (16 %) for atrial fibrillation (84 %) or thromboembolic disease (16 %). Serum DOAC concentrations were measured within 24 hours of the acute event, employing ultra-high performance liquid chromatography coupled with tandem mass spectrometry. We converted all measured concentrations to standardized trough levels. Anti-factor Xa activity was determined using a chromogenic assay.

Results: Sixty-four patients had a verified ischemic cerebrovascular event (stroke or TIA). Thirty had other diagnoses (most often orthostatic hypotension, dizziness, non-specific dysphasia/aphasia, migraine with aura, or epilepsy), and served as a control group. Eight patients with hemorrhagic stroke were excluded from the statistical comparisons. DOAC concentrations were significantly lower in those with a verified ischemic cerebrovascular event than in the control group (mean ± standard deviation: 255 ± 155 vs. 329 ± 144 nmol/L; p=0.029), despite no statistically significant difference in self-reported adherence and daily dosages. Levels ranged from 5.4 to 596 nmol/L in the ischemic stroke group and from 41 to 602 nmol/L in the control group. Concentration/dose ratios of DOACs and anti-factor Xa activity were both significantly lower in the ischemic stroke group than in the control group (p=0.028 and p=0.017, respectively). There were high correlations between DOAC serum concentrations and the anti-factor Xa activity both in the ischemic stroke group (r=0.96; p<0.001) and in the control group (r=0.85; p<0.001). CHA2DS2-VASc score was significantly higher in the ischemic stroke group than in the control group (4.9 ± 1.6 vs. 4.1 ± 1.7; p=0.007).

Discussion and Conclusion: Patients suffering from ischemic stroke had a more unfavorable cerebrovascular risk profile, and lower DOAC concentrations despite no evidence of reduced self-reported adherence. Although speculative, one could hypothesize that patients with high cerebrovascular risk might benefit from higher DOAC serum concentrations than those with a lower risk, potentially allowing for more precise and individualized dosing of DOACs. Although we found no

differences between groups in self-reported adherence, patient adherence should always be assessed before a dose increase is considered.

Busulfan Interlaboratory Proficiency Testing Program reveals worldwide errors in Drug Quantitation and Dose Recommendations

PhD, PharmD Dina Kweekel[1,2], PhD, PharmD Jeannine McCune[3], BS Arjen Punt[4,5], PhD, PharmD Matthijs Van Luin[2,6], PhD, PharmD Eric Franssen[2,7]
[1]Leiden University Medical Centrer, dept of Clinical Pharmacy and Toxicology, Leiden, the Netherlands, [2]Drug Analysis and Toxicology division of the Dutch Foundation for Quality Assessment in Medical Laboratories (SKML), Utrecht, the Netherlands, [3]Department of Hematologic Malignancies Translational Sciences and Department of Hematologic Malignancies & HCT, Beckman Research Institute at City of Hope, Duarte, USA, [4]Department of Clinical Pharmacy, Division of Laboratory Medicine and Pharmacy, University Medical Center Utrecht, Utrecht, the Netherlands, [5]Central Diagnostic Laboratory, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands, [6]Department of Clinical Pharmacology, University Medical Center Utrecht, Utrecht, the Netherlands, [7]Department of Clinical Pharmacy OLVG, Amsterdam, the Netherlands

Oncology, Møterom 2, september 25, 2023, 13:00 - 14:30

Background: Clinical outcomes of busulfan-based conditioning regimens for hematopoietic cell transplant (HCT) are improved by personalizing busulfan doses to target a narrow busulfan plasma exposure. We developed an interlaboratory proficiency test program for the quantitation, pharmacokinetic modeling, and dosing of busulfan in plasma. Previous (i.e., the first 2) proficiency rounds found that 67 to 85% were inaccurate, and 71 to 88% of the dose recommendations were inaccurate. Here, we present the results from the subsequent 5 busulfan proficiency test rounds.
Methods: a proficiency test scheme has been developed by the Dutch Foundation for Quality Assessment in Medical Laboratories (SKML) and consisted of 2 rounds per year, each round containing 2 busulfan samples. The current manuscript evaluates the subsequent five proficiency tests.
The busulfan proficiency samples are shipped without dry ice by stabilizing busulfan in N,N-dimethylacetamide. In each round, participating laboratories (labs) reported their results for two proficiency samples (i.e., a low and high busulfan concentration) and a theoretical case assessing their pharmacokinetic modeling and dose recommendations. Descriptive statistics were performed, with ±15% for busulfan concentrations and ±10% for busulfan plasma exposure and dose recommendations deemed accurate.
Results: Since January 2020, 41 labs have participated in at least one round of this proficiency test. Over the five rounds, an average of 78% of busulfan concentrations were accurate. AUC calculations were accurate in 75-80% of the cases; whereas only 60-69% of dose recommendations were accurate. Compared to the first two proficiency test rounds (PMID 33675302, Oct 2021), the busulfan quantitation results are similar, but the dose recommendations worsened. Some labs repeatedly submit results that deviate more than 15% from the reference value.
Conclusions: The proficiency test shows persistent inaccuracies in busulfan quantitation, pharmacokinetic modeling, and dose recommendations. Additional educational efforts have yet to be implemented; regulatory efforts appear to be needed. The use of specialized busulfan pharmacokinetics labs or sufficient performance in the busulfan proficiency test should be required for HCT centers prescribing busulfan.

UGT1A1 polymorphism and baseline bilirubin levels in predicting the risk of lipid disturbances in schizophrenia patients after antipsychotic treatment

Hualin Cai[1]
[1]The Second Xiangya Hospital of Central South University, Changsha, China

Psychiatry, Møterom 4, september 25, 2023, 13:00 - 14:30

Introduction
Maximizing symptomatic relief whilst minimizing side effects is the aim of treatment for schizophrenia with antipsychotic drugs. However, long-term use of atypical antipsychotic drugs (AAPD) often causes metabolic side effects in schizophrenia patients, which not only restricts the treatment strategy from the psychiatrists, but also reduces the compliance and life quality of patients, which in turn causes heavy economic burdens of family and society. Recent studies indicate that endogenous bilirubin plays an important role in regulation of lipid metabolism homeostasis. In the present study, we aim to investigate how post-treatment lipid disturbances can be predicted by pre-treatment bilirubin levels and related genetic variations.

Materials and Methods
There were 644 schizophrenia patients enrolled from two centers. We retrospectively collected the patients' clinical data from Center 1 (Total: 406, Male/Female 254/152) to explore the interrelationship among serum bilirubin levels, the usage of AAPDs and lipid metabolism parameters. Meanwhile, another cohort of patients were gathered from Center 2 (Total: 238, Male/Female 121/117) to validate the results From Center 1, and to further test the combinational predictive value of bilirubin gene polymorphisms and baseline serum bilirubin levels for the risk of developing lipid metabolic side effects during treatment. For the genotyping, a multiple PCR targeted capture technique was used to sequence the two cross-talked pathways including bilirubin metabolism-related genes (HMOX1, UGT1A1, SLCO1B1) and lipid metabolism-related genes (PGRMC1, INSIG1, INSIG2, SREBP1, SREBP2).

Results
For comparative and correlation analyses, it was found that: (1) there were no significant differences in baseline levels of serum bilirubin or lipid related indexes among different patterns of AAPDs including monotherapy along with combination treatment from two centers, (2) as compared with first-episode schizophrenia patients, relapsed schizophrenia patients had lower levels of serum bilirubin and higher levels of serum lipids at baseline, (3) after 4 weeks of AAPD treatment, the serum bilirubin levels significantly decreased and were negatively correlated with post-treatment serum triglyceride and cholesterol, and (4) the UGT1A1 rs4148323 (UGT1A1*6) mutation could lead to its reduced activity in converting indirect bilirubin (IBIL) to direct bilirubin (DBIL), resulting in significant elevation of IBIL and total bilirubin (TBIL). For the predictive analyses, it was demonstrated that: (1) among the three types of bilirubin, the parameter of pre-treatment DBIL was most powerful in prediction of post-treatment dyslipidemia in the ROC analysis (AUC=0.627, $p<0.001$), (2) multivariate logistic regression analysis showed that the UGT1A1*6 polymorphism was a strong protective factor for lipid metabolism, and (3) the combination of baseline DBIL and UGT1A1*6 significantly improve the performance in predicting the risk of developing dyslipidemia after AAPD treatment (AUC=0.939, $p<0.001$).

Discussions and Conclusions
Yet compared with the UGT1A1*28 mutation, the UGT1A1*6 occurs at a much higher frequency in the Asians rather than in the Caucasians. Given that the spectrum of UGT1A1 variants varies markedly in different populations, relevant lipid metabolic side effects of AAPDs might differ amongst racial and ethnic populations. For Asian population, schizophrenia patients without UGT1A1*6

mutation and relatively high levels of serum bilirubin at baseline could be more vulnerable to AAPD-induced lipid disturbances.

Impact of Beta-lactam Therapeutic Drug Monitoring Using Clinical Case Studies

Dr. Paul Jannetto[1], Sara E. Ausman[2], Lindsay Moreland-Head[3], Christina G. Rivera[3], Andrew Rule[4], Omar M. Abu Saleh[5], Ryan W. Stevens[3], Rebecca J. Wessel[6], Erin Barreto[3]
[1]Mayo Clinic, Department of Laboratory Medicine & Pathology, Rochester, United States, [2]Mayo Clinic Health System, Department of Pharmacy, Eau Claire, United States, [3]Mayo Clinic, Department of Pharmacy, Rochester, United States, [4]Mayo Clinic, Division of Nephrology and Hypertension, Rochester, United States, [5]Mayo Clinic, Division of Public Health, Infectious Diseases and Occupational Medicine, Rochester, United States, [6]Mayo Clinic, Strategy Department, Rochester, United States

Anti-infectives 1 - antibiotics and antifungals, Sal B, september 25, 2023, 13:00 - 14:30

Introduction:
In critically ill patients, beta-lactam antibiotics exhibit highly variable pharmacokinetics (PK) which leads to unpredictable therapeutic and toxic effects. Recently, a beta-lactam therapeutic drug monitoring (TDM) program to improve precision pharmacotherapy was launched. This report outlines the TDM program and two illustrative cases of real-world impact.
Materials and Methods:
Beta-lactam TDM was available for select critically ill adults (≥18 years) treated with cefepime, piperacillin/tazobactam, or meropenem. Eligible individuals included those on extracorporeal membrane oxygenation (ECMO), continuous kidney replacement therapy, or at extremes of weight. Steady-state peak and trough concentrations were performed with the target of a total serum drug concentration above the minimum inhibitory concentration (MIC) for the organism for the full dosing interval (100%T>MIC). In empiricism, this corresponded to a trough of at least 8 mcg/mL for cefepime, 16 mcg/mL for piperacillin, and 2 mcg/mL for meropenem (the MIC breakpoints for Pseudomonas aeruginosa) or a target tailored to the individual's observed microbiology. A validated liquid chromatography tandem mass spectrometry was used to measure drug concentrations and a PK calculator was developed to assess target attainment. Comprehensive education was also provided to clinical staff.
Results:
Case#1: A 30-year-old male chronically mechanically ventilated was admitted for acute hypoxic respiratory failure and suspected ventilator-associated pneumonia. At baseline he was colonized with multidrug-resistant organisms and had a serum creatinine of 0.61 mg/dL (normal: 0.74-1.35). The patient had baseline neurocognitive abnormalities including myoclonus which rendered a safety assessment of cefepime adverse effects (i.e., neurotoxicity) challenging. As part of a broad-spectrum antimicrobial regimen he was initiated on cefepime 2g intravenous (IV) twice daily as a 30-minute infusion and steady state concentrations were collected. Peak concentration was 50.7 mcg/mL and trough concentration was 8.1 mcg/mL resulting in a calculated T>MIC of 80-90% (below target). The PK calculator estimated that a dose modification to 2g every eight hours as a 30-minute infusion or 1g every eight hours as a 3-hour infusion would each improve the T>MIC to at least 100%. To minimize safety concerns with higher drug doses given baseline comorbidities, cefepime 1g IV every 8 hours was selected.
Case#2: A 36-year-old male presented the Emergency Department after a drug overdose and witnessed aspiration. His course was complicated by hypoxic and hypercapnic respiratory failure ultimately requiring intubation, mechanical ventilation, and ECMO. Broad spectrum antimicrobials were initiated for suspected sepsis of unknown primary etiology. Given evident augmented renal clearance a meropenem dose of 1g IV every eight hours as a 3-hour infusion was selected. Steady state peak and trough meropenem concentrations were 2.9 mcg/mL and <0.5 mcg/mL, respectively (T>MIC of 63%). The dose was increased to 2g IV every eight hours as a 3-hour infusion, with the potential to shorten the interval.
Discussion and Conclusions:

The beta-lactam TDM program was launched to improve precision pharmacotherapy in critically ill patients. These illustrative cases demonstrate how TDM can be leveraged to improve target attainment in this population with high PK variability. Individualized PK assessments allowed for deliberate decisions about dose adjustments that simultaneously balance effectiveness and safety.

Assessment of the status of thiamine and the alcohol biomarker phosphatidylethanol 16:0/18:1 in the Belgian adult population using volumetric absorptive microsampling: results from the Belgian Food Consumption Survey

Ms. Liesl Heughebaert[1], Dr. Katleen Van Uytfanghe[1], Dr. Nicolas Berger[2], Prof. Christophe Stove[1]
[1]Laboratory of Toxicology, Ghent University, Ghent, Belgium, [2]Department of Epidemiology and Public Health, Sciensano, Brussels, Belgium

Alternative sampling strategies 2, Møterom 1, september 26, 2023, 13:00 - 14:30

Background: To date, determination of the nutritional status of a certain population has mainly been achieved by the collection of data (e.g. dietary habits) via questionnaires or interviews. However, such data only allow to estimate - and do not directly quantify - a person's nutritional status. In that perspective, volumetric absorptive microsampling (VAMS) using Mitra™ devices allows for the convenient self-sampling of biological matrices at home, and, consequently, to accurately quantify nutritional status at a population level.
Materials and methods: As part of the third Belgian Food Consumption Survey, running from March 2022 to June 2023, the aim was to collect VAMS samples from over 1000 adult volunteers via finger prick for the determination of thiamine status and the alcohol biomarker phosphatidylethanol 16:0/18:1 (PEth). In addition, demographics and self-reported data on alcohol and food consumption were collected. Furthermore, the quality of the sampling was evaluated visually and by comparing the results obtained using replicates.
Results: Currently, VAMS samples of 462 participants (response rate of 60%) are included in the study of which the majority (55%) had PEth levels below 20 ng/mL, i.e. the cut-off for compatibility with abstinence. Approximately 40% of the participants could be considered "social drinkers" as their PEth levels were between 20 and 200 ng/mL. For thiamine, 10% and 2% of the participants had thiamine levels respectively below and above the reference range for an adequate thiamine status, i.e. 30 – 70 ng/mL. Finally, with respect to sample quality, 89% of the samples passed the visual quality check. Replicate analysis showed that concentrations of only a minimal number of replicates deviated more than 15%. As this is an ongoing study, data are still collected and updated graphs and extended data analysis results will be presented at the conference.
Conclusion: Using VAMS devices to self-sample at home, data on thiamine status and the alcohol biomarker PEth were collected, indicating an overall adequate thiamine status and a low to moderate alcohol consumption in the participants included in this survey.

Application of non-contact hematocrit prediction technologies to overcome hematocrit effects on immunosuppressant quantification from dried blood spots

Dr. Sigrid Deprez[1], Ms. Liesl Heughebaert[1], Ms. Laura Boffel[1], Prof. Christophe Stove[1]
[1]Laboratory of Toxicology, Ghent University, Ghent, Belgium

Alternative Sampling Strategies 1, Møterom 1, september 25, 2023, 13:00 - 14:30

Background: Fully automated dried blood spot (DBS) analysis for therapeutic drug monitoring (TDM) of immunosuppressants suffers from a so-called hematocrit (hct) effect. Being intrinsic to automated DBS analysis, this poses a serious drawback for accurate immunosuppressant quantification. Knowledge of a sample's hct allows to correct for this. The aim of this study was to investigate the validity of a correction algorithm during fully automated DBS analysis of immunosuppressants, based on knowledge of the DBS' hct, obtained via two distinct non-contact hematocrit prediction strategies, using either near-infrared (NIR) or ultra-violet/visible (UV/VIS) spectroscopy.
Materials and methods: For tacrolimus, sirolimus, everolimus, and cyclosporin A, 48, 47, 58 and 48 paired venous whole blood and venous DBS patient samples were collected, respectively, and analyzed using an automated DBS-MS 500 HCT extraction unit coupled to a liquid chromatography tandem mass spectrometry system. Additionally, for all 201 samples the hct of the DBS was predicted based on NIR and UV/VIS spectroscopy.
Results: For tacrolimus and cyclosporin A, both hct prediction strategies allowed for adequate correction of the hct effect as all 95% CIs of the slopes of the linear regression analyses after correction included zero. Also for sirolimus and everolimus the results greatly improved after hct correction, although a hct bias remained for sirolimus (95% CI -2.08 to -0.70 and -1.92 to -0.68, using NIR- and UV/Vis-based prediction, respectively), while for everolimus a slightly significant hct effect was observed after NIR- and UV/Vis-based correction (95% CI -1.00 to -0.24 and -0.76 to -0.01, respectively). Nevertheless, application of both hct prediction strategies ensured that clinical acceptance limits (i.e. ≥80% of the samples within 20% difference compared to whole blood) were met for all analytes: 95.8%, 97.7%, 83.3% and 87.5% using NIR-based hct prediction and 93.8%, 100%, 88.1% and 89.3% using UV/VIS based hct prediction for tacrolimus, cyclosporin A, sirolimus and everolimus, respectively.
Conclusion: In conclusion, we demonstrated that non-contact hct prediction strategies, applied in tandem with fully automated DBS analysis, can be used to adequately correct immunosuppressant concentrations, yielding a good agreement with whole blood.

Analytical validation and clinical application of a Volumetric Absorptive Microsampling method for Therapeutic Drug Monitoring of the oral targeted anti-cancer agents abiraterone, alectinib, cabozantinib, imatinib, olaparib and sunitinib and their metabolites

MSc Marinda Meertens[1], BSc Niels de Vries[1], Dr. Neeltje Steeghs[2], Dr. Hilde Rosing[1], Prof. Jos Beijnen[1,3], Prof. Alwin Huitema[1,4,5]

[1]Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands, [2]Department of Clinical Pharmacology, Division Medical Oncology, The Netherlands Cancer institute, Amsterdam, The Netherlands, [3]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands, [4]Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands, [5]Department of Pharmacology, Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

Alternative Sampling Strategies 1, Møterom 1, september 25, 2023, 13:00 - 14:30

Introduction: Volumetric Absorptive Microsampling (VAMS) is a useful tool for the application of Therapeutic Drug Monitoring (TDM) of oral targeted anti-cancer agents, with the ultimate goal of preventing unnecessary toxicity and improving efficacy. TDM with VAMS allows collection of blood samples at home by patients themselves avoiding a visit to the outpatient clinic. Moreover, blood sampling with the finger prick technique is less invasive for patients and saves personnel time. A particular advantage of using VAMS is the stability of analytes given the dried form and the claimed analyte recovery independence of haematocrit. The aim of this study was to develop and validate an UHPLC-MS/MS quantitation method for the determination of abiraterone, alectinib, cabozantinib, imatinib, olaparib, sunitinib, and metabolites Δ(4)-abiraterone (D4A), alectinib-M4, imatinib-M1 and N-desethyl sunitinib in VAMS to support TDM. Additionally, the validated method will be applied to identify the VAMS-to-plasma ratio and to evaluate the patient feasibility of collecting whole blood samples using VAMS devices.

Methods: After collection of 10 µL whole blood samples using VAMS devices (MitraTM, Neoteryx, (Torrance, CA, USA)), the compounds were extracted from the tip with methanol while shaking with grinding balls (3.96 mm), evaporated with nitrogen and reconstituted in ACN : 100 mM NH4OH in H20 (1:1, v/v). The extracts were injected on a LC-MS/MS system and separation was achieved on a C18 column using gradient elution. For detection, a Sciex QTRAP6500 tandem mass spectrometer was used, operating in the positive ion mode. Validation experiments based on the EMA guidelines were carried out and stability was tested under shipping- and storing conditions. VAMS samples were collected after a venous blood draw, in order to compare plasma levels with the whole blood concentrations measured in the VAMS samples. Patients were also asked to perform a finger prick at home to evaluate the feasibility.

Results: The validated range of this method was considered accurate and precise from 2-40 ng/mL for abiraterone, 0.5-10 ng/mL for D4A, 100-2000 ng/mL for alectinib and cabozantinib, 50-1000 ng/mL for alectinib-M4 and imatinib-M1, 200-4000 ng/mL for imatinib, 400-8000 ng/mL for olaparib and 5-100 ng/mL for sunitinib and N-desethyl sunitinib. Executed validation experiments fulfilled the requirements. Stability data allows the shipment within 14 days at room temperature and storage of the VAMS sponges up to 12 months at -20 and -70°C. To date, samples from 49 patients were collected in the hospital, of which 43 were willing to collect a set of two VAMS samples at home. Of the patients who returned samples, 4.2% failed to draw both samples correctly, 29.2% collected 1 properly-filled device and 66.7% managed to draw both samples successfully, indicating promising feasibility.

Conclusion: The developed method was able to successfully quantify concentrations of abiraterone, alectinib, cabozantinib, imatinib, olaparib, sunitinib, and metabolites D4A, alectinib-M4, imatinib-M1 and N-desethyl sunitinib in VAMS samples within the validated range. VAMS collection at home was feasible for patients and more data is needed to complete the clinical validation to estimate the VAMS-to-plasma ratios.

Limited sampling strategies to estimate tacrolimus whole blood, total plasma and free plasma exposure.

BSc Diwa Masoud[1], PhD Amelia R. Cossart, PhD Nicole M. Isbel, PhD Scott B. Campbell, Brett McWhinney, PhD Christine E. Staatz
[1]School of Pharmacy, University of Queensland, Brisbane, Australia

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction: Therapeutic drug monitoring (TDM) of tacrolimus is normally based on whole blood trough concentration (C0) values. However, full dose-interval area-under-the-concentration-time curve (AUC0-12) estimation gives a more accurate estimation and quantification of free tacrolimus concentrations in plasma may better reflect drug pharmacological activity than measurement of whole blood concentrations. Limited sampling strategy (LSS) is a practical way in which AUC0-12 can be estimated without full pharmacokinetic profiling. The aim of this study was to develop LSSs to estimate whole blood, total plasma and free plasma tacrolimus AUC0-12 in adult kidney transplant recipients.
Materials and methods: Whole blood, total plasma and free plasma tacrolimus AUC0-12 were collected from 22 elderly, adult kidney transplant recipients. AUC0-12 based on LSSs were compared to that estimated by the linear trapezoidal method. The predictive performance was assessed by calculating the median percentage prediction error (MPPE) and median absolute prediction error (MAPE).
Results: AUC0-12 estimates using LSS equations based on whole blood, total plasma and free plasma measurements taken at 0, 1-, 2- and 4-hours post-dose were strongly correlated with AUC0-12 estimates based on full pharmacokinetic profiling. Predictive performance was acceptable across all three mediums with a MPPE of 0.3%, 0.1% and 0.1% and a MAPE of 3.1%, 6.8% and 7.2% respectively, for whole blood, total plasma and free plasma measurement.
Discussion and conclusion: LSSs, based on drug measurement in the first 4-hours post-dose, provide a reliable estimation of tacrolimus AUC0-12 in whole blood, total plasma and free plasma mediums in elderly adult kidney transplant recipients.

Pharmacodynamics of rituximab and its biosimilars on CD19+ B lymphocytes in pediatric patients with complex diseases

Phd Natalia Riva[1], PharmD Lucas Brstilo, PharmD Aymara Sancho Araiz, BSc Manuel Molina, MD Andrea Savransky, PharmD Paulo Cáceres Guido, MD Silvia Tenembaum, MD Maria Martha Katsicas, PhD Iñaki F Troconiz, PhD Paula Schaiquevich
[1]Pharmacometrics and Systems Pharmacology Department of Pharmaceutical Technology and Chemistry, Pamplona, Spain

Biologicals, Sal B, september 26, 2023, 13:00 - 14:30

Introduction/Aim. Limited pharmacotherapy and the failure of conventional treatments in complex pathologies such as neuromyelitis optica and systemic lupus erythematosus lead to the increasing use of rituximab and its biosimilars. Especially in pediatrics, off-label indications of rituximab are frequent due to methodological difficulties, ethical reasons, and a lack of clinical studies. In this work, we aimed to characterize semi-mechanistically the time course of CD19+ B lymphocytes under treatment with rituximab evaluating the impact of different clinical, pharmacological, and drug-related covariates on rituximab pharmacodynamics and clinical response in children with neurologic and autoimmune diseases.
Methods. A retrospective study was conducted between January 2019 and December 2021 in paedriatic patients who were treated with rituximab for neurologic or autoimmune diseases at Hospital JP Garrahan (Argentina). Pre- and post- drug infusion CD19+ lymphocyte counts in peripheral blood was registered. A kinetic-pharmacodynamic model for quantitative exposure-response evaluation was built, linked through an EMAX model (considering the effect of rituximab on the death rate of CD19+ lymphocytes). Demographic, clinical, pharmacological (including innovative and biosimilar formulations), and drug-related data were collected. Population analysis was performed with NONMEM v7.4. In addition, a logistic regression analysis was carried out in a subgroup of patients (n=26) to identify factors related to the development of an unsatisfactory clinical response (stable disease or no response using disease activity scores).
Results. In total, 63 children with autoimmune and neurologic diseases were included for model building after the first rituximab cycle (n=52) and for external exploration of the model during subsequent cycles (n=11). In total, 281 measurements of CD19+ lymphocyte counts were available out of which 137 (49%) were below the limit of quantification handled with the M3 method. Rituximab elimination rate constant (% relative standard error) (KE) was 0.06 days-1 (17%) and the CD19+ death rate (KOUT) was 0.004 days-1 (22%). Importantly, 22% of the patients underwent substitution between the innovator and biosimilar drug product. No association was found between any of the estimated parameters and covariates. External model exploration enabled the implementation of the current model in repeated administrations of rituximab.
Although no significant associations were identified between clinical response and covariates, a trend to an unsatisfactory response was observed in patients with lower CD19+ suppression times and higher areas under the CD19+ versus time curve.
Conclusions. The pharmacodynamics of rituximab were described in a real-world setting in Latin-American children suffering from complex diseases. Substitution between innovator rituximab and its biosimilars did not affect rituximab effects on CD19+ profiles nor the clinical response. Evaluation in larger pediatric cohorts and identification of relevant factors related to rituximab pharmacodynamics and clinical response may contribute to increasing high-quality scientific evidence in off-label rituximab treatments, using cost-effective biosimilars without compromising the efficacy.

Metabolomics Investigation of cyclosporine-Induced nephrotoxicity

Ph. D. Xiaoxue Wang[1], Mrs LI Pengmei[1], Ph. D. QIN Wei[1]
[1]China-japan Friendship Hospital, Beijing, China

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Cyclosporine A (CsA) is a very important immunosuppressive agent that greatly improves the survival rates of patients and grafts after solid-organ transplantation. However, CsA nephrotoxicity is a serious side effect that limits the clinical use of CsA. This study aimed to utilize human plasma samples to investigate the mechanism and biomarkers of CsA nephrotoxicity through a metabolomics approach. Patients that were administered CsA were classified into a CsA induced nephrotoxicity group and control group. Plasma samples were analyzed by metabolomics using ultra-performance liquid chromatography coupled with Obitrap mass spectrometry. The obtained peak areas for each metabolite were utilized for multivariate statistical analysis, fold change evaluation, and univariate statistical tests to identify metabolites. This study showed a significantly lower glycine (p =2.41E-19) and a higher L-carnitine (p = 5.95E-13) in the CsA induced nephrotoxicity group. Through logistic regression analysis, the formula for predicting CsA nephrotoxicity is Y =0.019208 * L-carnitine - 0.016006 * glycine+2.9298. Changes in the levels of these metabolites indicated that amino acid metabolism and energy metabolism were disturbed with CsA associated nephrotoxicity, which may provide novel and promising research approaches to CsA nephrotoxicity.

Comparison of imprecision and accuracy between standard DBS and volumetric DBS for measuring PEth

PhD Mikael Ström[1], Professor Olof Beck, Christer Wallin
[1]Capitainer AB, Solna, Sweden

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

1. Introduction

Phosphatidylethanol (PEth) is an alcohol biomarker with unique properties that reflects recent weeks exposure to alcohol. PEth has been measured predominantly in whole blood collected by venous puncture. Decision limits are applied to indicate abstention or risky drinking. In recent years there has been an interest to use capillary blood dried on a filter paper (DBS) as an alternative to venous puncture and to minimize the continued formation of PEth post sampling if ethanol is present. The presented work was performed to compare standard DBS with volumetric DBS (qDBS) regarding imprecision and accuracy.

2. Materials and Methods

Twenty-five individuals with self-reported alcohol drinking were recruited to provide capillary blood collected on DBS devices. One was the Whatman 903 Protein Saver card (stdDBS) and the other the Capitainer®BVanadate device (qDBS). The individuals were instructed to puncture the finger using the BD 2.0 mm contact-activated lancet after cleaning with a swab having 70% isopropyl alcohol as disinfectant. The blood from the finger was collected without any squeezing. One drop at the time was applied on the DBS devices. On total 5 drops were applied on a Protein Saver card and 4 on 2 qDBS devices. The qDBS device provided ready to use 10.0 µL dried blood specimens on 6 mm discs and the Protein Saver cards were punched with a 6 mm punch in the center of the blood spot. PEth was analysed using a published LC-MS/MS method using PEth-d5 as internal standard and isopropanol for extraction. The total imprecision of the method was <9%.

3. Results

In twelve cases 4 discs and in 5 cases 3 discs were obtained with the qDBS device which had PEth concentrations between 0.05 and 0.51 µmol/l. The calculated imprecision (CV) within replicate spots ranged from 0.29 to 9.6%, with a mean of 4.6%. For stdDBS the blood volume was assumed to be 12.84 µL based on Moat and coworkers§. The number of cases where 4 spots were obtained was 23. The calculated imprecision within replicates ranged from 2.4 to 38.6%, with a mean of 11.0%. In addition for std DBS, there was a bias in the measurement based on the assumed blood volume of a punched subsample. The uncertainty was estimated by comparing the mean values from stdDBS and qDBS for each individual and by using the qDBS as reference value for 10 µL. This contribution to uncertainty was estimated to 7.5%. By combining the 2 sources of uncertainty assuming their independence a value of total imprecision of 13.3% was estimated. In addition, the results indicated a mean blood volume on the 6 mm punch from stdDBS of 11.3 µL.

4. Discussions and Conclusions

PEth measurement is a good example where accuracy and precision are fundamental. By using a volumetric DBS the accuracy and precision can be significantly improved. The Capitainer®B Vanadate volumetric BDS device also offer the advantage ascertain PEth stability post-sampling by having a Phospholipase D inhibitor incorporated.

§Reference: Moat SJ et al. Ann Clin Biochem. 2021;58:123

The dietary CYP2D6 activity marker solanidine predicts risperidone clearance well and may improve model informed precision dosing of CYP2D6 substrates

MSc Birgit Wollmann[1], Dr Marianne Kristiansen Kringen[1,2], Dr Robert Løvsletten Smith[1], Prof. Magnus Ingelman-Sundberg[3], Prof. Espen Molden[1,4], Dr Elisabet Størset[1]
[1]Centre For Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway, [2]Department of Life Science and Health, OsloMet – Oslo Metropolitan University, Oslo, Norway, [3]Department of Physiology and Pharmacology, Section of Pharmacogenetics, Karolinska Institutet, Stockholm, Sweden, [4]Department of Pharmacy, University of Oslo, Oslo, Norway

Pharmacometrics, Møterom 5, september 25, 2023, 13:00 - 14:30

Introduction

The individual dose requirement of CYP2D6 substrates varies considerably. Although CYP2D6 genotype explains some of the variability, the unexplained variability remains large. Solanidine is a dietary compound that is measurable in serum, metabolized by CYP2D6, and recently reported as a potential CYP2D6 activity marker. In this study, we used the population approach to describe the pharmacokinetics of the CYP2D6 substrate risperidone and evaluated solanidine metabolic ratio and CYP2D6 genotype as candidate covariates to predict risperidone clearance.

Materials and Methods

Data were retrieved from the pharmacogenetics and therapeutic drug monitoring databases at Center for psychopharmacology, Diakonhjemmet Hospital. Initially, 133 CYP2D6-genotyped subjects without co-treatment with interacting drugs contributed 255 serum concentrations measurement pairs for risperidone and its major metabolite 9-hydroxyrisperidone. Solanidine and metabolite (3,4-seco-solanidine-3,4-dioic-acid) measurements were available from the same blood samples. Six samples (2%) were excluded due to undetectable solanidine and metabolite, leaving 131 subjects and 249 samples for population pharmacokinetic analysis.

The data were described using a one-compartment model with first-order absorption and transfer into a metabolite compartment with age-dependent clearance, informed by previous reports for risperidone. The following covariates were included on risperidone apparent clearance (CL/F) in two candidate models: i) CYP2D6 genotype (translated into phenotype: poor, intermediate and normal metabolizers), and ii) the ln-transformed ratio between semi-quantitatively determined solanidine metabolite and parent solanidine concentration. The improvement in model fit for each covariate was assessed using the likelihood ratio test (i.e. difference in objective function value, OFV).

The models were also externally evaluated by using population parameters and covariates to predict individual risperidone clearance in a second dataset consisting of 87 subjects. They were compared visually and numerically by summarizing median prediction error (ME) and median absolute prediction error (MAPE) as measures of bias and imprecision, respectively.

Results

In the covariate-free base model, risperidone typical CL/F were estimated to 18 L/h, with 94% [CV] between-subject variability (BSV). Inclusion of CYP2D6 genotype as covariate improved the model fit significantly (OFV −28, $p<0.0001$). The model-estimated risperidone CL/F in poor, intermediate and normal metabolizers were 5, 12 and 23 L/h, and risperidone unexplained BSV was lowered to 80%. However, inclusion of solanidine metabolic ratio as covariate led to a markedly more pronounced improvement of the base model fit (OFV −81, $p<0.0001$). An exponential function was superior to a

linear function, and it predicted risperidone CL/F of 5 L/h to 47 L/h across the range of solanidine metabolic ratios (ln: −10 to 6). With this model, risperidone unexplained BSV was lowered to 57%.

The solanidine-based model predicted risperidone clearance well in an external data set (ME +5%, MAPE 32%), and slightly more accurately and precisely than the CYP2D6 genotype-based model (ME −12%, MAPE 37%).

Discussions and Conclusions

Measurements of solanidine and its metabolite in serum allows more precise predictions of individual risperidone clearance as they reflect more sources of CYP2D6 variability than CYP2D6 genotype alone. Solanidine is a promising dietary CYP2D6 marker that should be further evaluated for its potential role in model informed precision dosing of CYP2D6 substrates.

Overcoming institutional barriers to AUC-guided dosing of vancomycin: a quality improvement project

Dr. Lena Aronsen[1], Dr. Vilde Lehne Michalsen[1]
[1]Department of Laboratory Medicine, Diagnostic Clinic, University Hospital of North Norway, Tromsø, Norway

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction

Traditionally vancomycin is dosed by aiming for trough values between 15-20 mg/L. International guidelines recommend area under the curve (AUC)-guided dosing, preferably by Bayesian software, in order to minimize vancomycin-induced nephrotoxicity. Implementation of AUC-guided dosing can be challenging due to institutional barriers. Using quality improvement (QI) methodology, we aimed to identify and overcome these barriers at the University Hospital of North Norway.

Materials and Methods

We formed a team comprising three medical doctors within clinical pharmacology and infectious diseases, two pharmacists, a nurse and a biomedical laboratory scientist. We gathered feedback from various stakeholders and emphasized education regarding the software and vancomycin pharmacokinetics. Using various QI tools (e.g. PDSA-cycles), we identified barriers throughout the entire workflow, i.e., communication between clinicians and the laboratory, blood sampling procedures and decision-making regarding dose adjustment. We ran PDSA-cycles to test and optimize the workflow. The aim of the project was that at least 50 % of patients receiving vancomycin at the infectious disease ward should have at least one Bayesian AUC estimation during the first 6 months of 2023.

Results

We identified four main barriers to implementation of AUC-guided dosing of vancomycin at our hospital. First, we addressed the knowledge gap regarding vancomycin AUC, informing the various stakeholders about the advantages of Bayesian dosing. In order to minimize effort for the medical doctors at the infectious diseases ward, we offered that trained clinical pharmacologists at the laboratory could perform the AUC estimation at their requests. Second, there was no formal way for the medical doctors to request AUC-guided dosing from the laboratory. Therefore, we set up an analysis named “s-vancomycin AUC” in the electronic health record (EHR) that selected medical doctors could request. The AUC estimation and dosing recommendation was then documented in the EHR. Third, neither local nor national guidelines were recently updated and did not recommend AUC-guided dosing of vancomycin. Thus, we emphasised that AUC-guided dosing recommendations can be a support for clinical decision making, and not necessarily replace traditional trough-based dosing. Fourth, the cloud-based Bayesian software had data privacy issues and required extensive training. We solved the privacy issues by de-identifying personal health information submitted to the software. Finally, we tested the software extensively and developed a standard operating procedure with a set of written instructions that describes the step-by-step process. During the first three months of the project 85 % of patients (n=7) receiving vancomycin at the infectious disease ward had at least one Bayesian AUC estimation.

Discussions and Conclusions

We conclude that small scale implementation of AUC-guided dosing of vancomycin in selected patients is possible. Larger scale implementation will require extensive education and training of medical doctors and pharmacists. Future perspectives include validating the AUC estimation in our population and expanding the service to all departments at our hospital and other hospitals within the regional health authority. We also plan post implementation research to evaluate benefits of AUC-guided dosing of vancomycin.

Ruxolitinib (RUX) pharmacokinetics (PK) in hematopoietic stem cell transplant (HSCT) children with chronic graft-versus-host disease (cGVHD) refractory to steroid therapy.

Audrey Denoncourt[1], Dr. Thai Hoa Tran[2], Dr. Paul Gavra[3], Dr. Michel Duval[2], Dr. Pierre Teira[2], Dr. Tiago Nava[2,3], PhD Valérie Villeneuve[1], PhD Yves Théorêt[1,3], Dr. Henrique Bittencourt[2]
[1]Pharmacology Research Unit, Research Center CHU Sainte-Justine, Montreal, Canada, [2]Division of Pediatric Hematology/Oncology, Department of Pediatrics, Charles-Bruneau Cancer Center, CHU Sainte-Justine, Montreal, Canada, [3]Clinical Pharmacology Laboratory, OPTILAB CHU Sainte-Justine, Montreal, Canada

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction. cGVHD is a life-threatening complication occurring in up to 70% of allogeneic HSCT patients and is one of the leading causes of remission death with a 5-year survival rate from 30 to 50%, mainly due to immune dysregulation and infections. Corticosteroids in association with a calcineurin inhibitor are the standard of care for GVHD management, but about half of patients are corticosteroid-refractory or corticosteroid-dependent. For those patients, RUX is a new, well-tolerated treatment option that can reduce disease symptoms and improve quality of life. However, a broad range of factors such as genetics, food intake and use of concomitant medication are variables known to influence kinase inhibitors' PK. Changes in body composition, body size, maturation of organ functions, drug formulation and treatment compliance are additional and unique considerations contributing to PK variability in pediatric patients. The aims of the current study were to measure RUX plasma concentrations in children and young adults with cGVHD and to develop an algorithm for optimization of its dosing regimen.
Material and methods. RUX was measured using a validated high performance liquid chromatography method coupled to tandem mass spectrometry as per regulatory agencies guidelines. In brief, after protein precipitation of samples with methanol containing RUX-d9, chromatographic separation was achieved on a Phenomenex Kinetex® C18 2.6 µm (2.1 × 50 mm) column using a mobile phase gradient (10 mM ammonium acetate and 1% formic acid and variable proportion of water and methanol) running at a flow rate of 250 µL/min. Total run time was less than 9 min/sample. Detection was performed under positive-electrospray-ion multiple reaction monitoring mode using 307.2 → 186.0 and 316.3 → 186.0 transitions for RUX and RUX-d9, respectively.
Results. RUX calibration curves were linear in the concentration range from 0.98 to 1000 ng/ml with correlation coefficients r > 0.999. RUX plasma levels were measured in 229 samples collected from 20 patients: 14 patients less than 12 years old (10 boys) with a median age of 2.5 years old and 6 patients between 12 and 21 years old (5 boys) with a median age of 15 years old. Using a limited sampling strategy, 39 and 12 AUC0-12h (area under the curve) were calculated for the <12 and >12 year-old groups, respectively. The median (range) AUC for those <12 years old was 314 ng.h/ml (93-1325 ng.h/ml) versus 430 ng.h/ml (194-915 ng.h/ml) for the older group. Median (range) trough concentrations for patients <12 years old and those >12 years old were 1.8 ng/ml (0.5-90 ng/ml) and 9.9 ng/ml (3.5-62 ng/ml), respectively.
Conclusion. Our data showed a wide intra-and inter-individual variability of key PK parameters, particularly in younger patients, and strongly support the use of therapeutic drug monitoring to optimize RUX dosing in children with cGVHD.

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A convenient method for TDM

Xiuli Xu[1], R&D Director Yujun Zhou[1]
[1]Beijing Diagreat Biotechnologies Co., Ltd, , China

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Instruction to the principle of Fluorescence Immunochromatographic Assay
Analysis of its main advantages and disadvantages:
Time-resolved fluorescence immunoassay (TRFIA) is a rapid detection method combining immunology and chromatography techniques. The supporting miniature fluorescence detector can realize quantitative detection with sensitivity reaching to pg/mL, apply to whole blood specimen, obtain the test results within 5-15 minutes, and store and transport at room temperature, which is very suitable for rapid point-of-care detection outside the central laboratory.

Materials and Methods:
Time-Resolved Immunofluorescence Analyzer, together with reagents of methotrexate, vancomycin, carbamazepine, and voriconazole from Diagreat.
The analytical performance of the above four reagents was evaluated and compared with mainstream TDM technology.

Results
The linear range of methotrexate was 0.05-20 uM, the intra-assay precision was less than 12%, and the correlation with LC-MS/MS was 0.95. The linear range of vancomycin was 0.5-50 ug/mL, the intra-assay precision was less than 12%, and the correlation with Abbott I2000 was 0.97. The linear range of carbamazepine was 0.5-20 ug/mL, the intra-assay precision was less than 13%, and the correlation with Abbott I2000 was 0.96. The linear range of voriconazole was 0.5-40 ug/mL, the intra-assay precision was less than 12%, and the correlation with LC-MS/MS was 0.96.

Discussion and Conclusion
The methotrexate, vancomycin, carbamazepine, and voriconazole Point-of-care Test method that established based on TRFIA is comparable to mainstream commercial TDM immunoassay reagents or LC-MS /MS in terms of accuracy, sensitivity and linear range. The intra-assay precision is obviously inferior to the reference method, but within an acceptable range, and it can meet the clinical needs. As the reagent can be stored at room temperature and the instrument is portable, small and convenient in application, it can be applied to a wider range of application scenarios compared with existing detection methods.

Adaption of an antiepileptic dried blood spot method for use in a clinical routine laboratory

Camilla Linder[1], Biomedicla Laboratory Scientist Sara Sadek[1], Phd, chemist Madeleine Pettersson Bergstrand[1], Phd, chemist Victoria Barclay[1]
[1]Medical Unit of Clinical Pharmacology, Medical Diagnostics Karolinska, Karolinska University Hospital, , Sweden

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction:
Dried blood spot is a matrix that can be used for therapeutic drug monitoring. Advantages, like capillary blood collection, easy transportation with regular mail and analyte stability on filter paper, makes it possible for patients to self-sample at home. The aim was to adapt a developed and validated dried blood spot liquid chromatography mass spectrometry research method for three common antiepileptic drugs, to routine clinical laboratory requirements. The new method should be robust and suited to the laboratory workflow.
Material and methods:
The method was simplified by replacing an eight-point calibration curve with a five-point curve for three analytes with three levels of internal controls.
External freeze-dried plasma control material from LGC (UK) replaced a part of the plasma volume in whole blood and was spotted onto filter paper. The aim was to produce external controls for dried blood spots (1).
Transfer of extracts to a new 96-well plate by a Hamilton robotic handler, was replacing a manual pipetting procedure. Intraday precision of three levels of controls were compared, n = 5/level.
Results:
Results showed that it was possible to reduce the number of calibrators to five, with good accuracy (within ±15%), precision (<15%) and R2-values ≥0.997 for all analytes.
From external controls (n=11/analyte), >80% were within ±15% of the nominal values.
Intraday precision (CV%) from three levels of controls/analyte was calculated for the manual method and the robotic transfer method. For carbamazepine, precision with the manual method was ≤6.1% and with the robotic method ≤5.6%. For lamotrigine it was ≤9.9% with the manual and ≤8.0% with the robotic method. Results for valproic acid was ≤3.9% with the manual and ≤5.7% with the robotic method. As both methods had intraday precisions ≤15% it was concluded that the robotic transfer method could replace the manual method, reducing risks of pipetting errors.
Discussion and conclusions:
The dried blood spot method (liquid chromatography mass spectrometry) for measuring concentrations of antiepileptic drugs was successfully adapted to clinical laboratory workflow. Patients with epilepsy have the possibility to choose self-sampling at home for therapeutic drug monitoring of common antiepileptic drugs. Awaiting external quality control-programs for dried blood spot methods, in-house made controls from external plasma material can be used.

1. Velghe S, Stove CP. Volumetric absorptive microsampling as an alternative tool for therapeutic drug monitoring of first-generation anti-epileptic drugs. Anal. Bioanal. Chem., 1–11 (2018).

Dried blood spot method for antiepileptic drugs in a clinical routine laboratory; implementation of pre- to postanalytical steps for a dried blood spot sample

Camilla Linder[1], Phd, chemist Victoria Barclay[1], Phd, MD Isabella Ekheden[2]
[1]Medical Unit of Clinical Pharmacology, Medical Diagnostics Karolinska, Karolinska University Hospital, Stockholm, Sweden, [2]Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction:
Antiepileptic drugs (AED) are used for treatment of epilepsy. Some of these drugs can give rise to pharmacokinetic interactions, affecting the concentration. For some patients, therapeutic drug monitoring is important to control effect and risk of adverse drug reactions. Living in isolated geographic areas, hindered mobility or sickness are reasons that hinder patients to get to a healthcare center for blood-sampling. Children and pregnant women also need frequent follow up of their AED concentrations. For these patients it might be more convenient to self-collect capillary blood on filter paper at home, sending it by mail to the laboratory. The last decades, many dried blood spot (DBS) methods were developed but few of them have been fully implemented.

The aim was to implement pre-to postanalytical steps for a validated DBS method, to clinical laboratory requirements.

Material and Methods:
Kit material for self-sampling (including instructions) could be ordered via Karolinska University Hospital internal service for customers. The physician decides to order DBS AED analysis in the electronic medical record system if considered suitable for the patient. The patient receives a print copy of the electronic order, including labels with the unique number-ID and a kit with sampling material. Education for DBS self-sampling is offered. The patient collects the DBS sample at home and fills in necessary information on the referral. The DBS sample is mailed to the laboratory according to instructions.
Envelope with the DBS sample is opened upon arrival and inspected by the laboratory staff following a checklist with criteria for acceptable sample quality. Hematocrit of the DBS sample is estimated with an office-scanner and Image analysis (1). The analysis is performed within a week with standard of procedures for quantification of AED in DBS.
The result is controlled by the clinical pharmacologist before approval. The prescribing physician receives the results as estimated plasma concentrations in the electronic system.
Results:
During 1.5 years as a routine method, 16 orders of AED concentrations reached the laboratory by mail. One sample was rejected because of too small sample volume. All samples had predicted hematocrits within the validated ranges for the analytical method and could be answered within a week from arrival.
Discussion and Conclusion:
The number of DBS samples during this period was small. One reason might be the lack of advertisement and information about the possibility to choose self-sampling at home. In this project there has not been a budget included for information to neurology departments. Physicians and patients may not know about the alternative DBS sampling. Another reason might be that the nurses have limited time to inform and educate patients for this procedure.
We managed to implement a laboratory routine for DBS and self-sampling at home for TDM of AED. In the future we want to apply for accreditation of the method and increase the advertising to customers and patients.

1. Barroso MG, Gustafsson L, Barclay V, Linder C. A validated method for the determination of hematocrit in dried blood spots using image analysis. Bioanalysis. Epub ahead (2023).

Model-informed precision dosing of intravenous busulfan in Thai pediatrics patients

Apichaya Puangpetch[1], Assistant Professor Dr. Fabienne Thomas[2], Associate Professor Dr. Usanarat Anurathapan[3], Professor Dr. Samart Pakakasama[3], Professor Dr. Étienne Chatelut[2], Professor Dr. Chonlaphat Sukasem[1], Mr. Félicien Le Louedec[2]
[1]Depaetment Of Pathology, Faculty Of Medicine, Mahidol University, Bangkok, Thailand, [2]Laboratoire de Pharmacologie, Institut Claudius-Regaud, Institut Universitaire du Cancer de Toulouse Oncopole, Centre de Recherche en Cancérologie de Toulouse, INSERM U1037, Université Paul Sabatier,, Toulouse, France, [3]Division of Hematology-Oncology, Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Pharmacometrics, Møterom 5, september 25, 2023, 13:00 - 14:30

Introduction
Intravenous busulfan is a cornerstone in conditioning regimens for pediatric hematopoietic stem cell transplantation. High systemic exposure is associated with clinical outcomes and hence the need for therapeutic drug monitoring (TDM). However, considerable interindividual variability in pharmacokinetics (PK) has been found. To achieve optimal busulfan exposure, (1) a covariate-based formula to predict busulfan clearance (CL) for a priori dose individualization and (2) an optimal model-based TDM strategy for a posteriori dose adjustments were determined.
Materials and Methods
The study was conducted retrospectively. One hundred fourteen Thai pediatric patients have been recruited. Busulfan concentration data collected during TDM of patients treated in Ramathibodi Hospital (Bangkok, Thailand) were modeled with a population approach (NONMEM 7.4, Icon PLC). Several methods for modeling the influence of the size of the patients were investigated: power model with the actual body weight (BW), power model with a varying exponent, or calculation of the normal fat mass. The influence of the following variables was screened with a stepwise covariate modeling procedure: actual age, age transformed with a maturation function, sex, malignant disease (MALIGN), fludarabine co-administration, genetic polymorphism of Glutathione S-transferase Alpha-1 (GSTA1, rs3957357 & rs3957356). A limited sampling strategy was explored using CL estimated from all concentration-time points as a reference. Finally, the days when TDM should be performed were assessed through simulations with the R packages mrgsolve and mapbayr. The day-by-day busulfan courses of 1,000 virtual patients for several TDM strategies were simulated, with all the sources of variability taken into account: covariate distribution, inter-individual (IIV), inter-occasion (IOV), and residual variabilities.
Results
A mono-compartmental model with proportional residual variability is best described with IIV and IOV on CL (26.0% and 14.1%, respectively) and on the volume of distribution (16.3% and 13.8%, respectively). The patient size was incorporated with a standard power model with actual body weight and a constant exponent. The covariate screening revealed that CL at day 1 was best predicted a priori with the following formula: CL = (BW/25)^0.786 * 0.896^MALIGN * 0.894^GSTA1. Three concentrations (0.25, 2, and 5 hours after the end of the infusion) were sufficient for a satisfactory Bayesian estimation of CL (relative root-mean-square error: 3.4%). Simulations showed that dose calculations based only on the covariate formula performed poorly: the 90% prediction interval of the cumulative AUC relative to the target AUC was 69-151%. In comparison, TDM-based calculations yielded more precise cumulative AUCs, whichever days the TDM was performed at: day 1 only (85-124%), day 1-3 (90-116%), and day 1-2-3 (93-112%).
Discussions and Conclusions
Population pharmacokinetic analysis of intravenous busulfan in Thai pediatric patients suggests that body weight, the decrease of CL on days 2-3-4, diagnosis, and GSTA1 are the common predictor of CL.

Moreover, this comprehensive approach quantified the benefit of TDM to control busulfan exposure in Thai pediatric patients and suggest to decrease the number of samples to 3 per day of TDM. A user-friendly shiny web application is now available for routine dose calculation.

Influence of DPYD gene polymorphisms on 5-Fluorouracil toxicities in Thai colorectal cancer patients

Dr. Chalirmporn Atasilp[1], Dr. Natchaya Vanwong[2], Miss Pavitchaya Yodwongjane[1], Dr. Phichai Chansriwong[3], Dr. Ekaphop Sirachainan[3], Dr. Thanyanan Reungwetwattana[3], Miss Pimonpan Jinda[5], Miss Somthawin Aiempradit[3], Miss Suwannee Sirilerttrakul[3], Dr. Monpat Chamnanphon[4], Dr. Apichaya Puangpetch[5], Dr. Patompong Satapornpong[6], Dr. Fabienne THOMAS-JEAN[7], Dr. Chonlaphat Sukasem[5]

[1]Thammasat University, Pathum Thani, Thailand, [2]Department of Clinical Chemistry, Faculty of Allied Health Sciences, Chulalongkorn University, , Thailand, [3]Division of Medical Oncology, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, , Thailand, [4]Department of Pathology, Faculty of Medicine, Srinakharinwirot University, Nakhonnayok, , Thailand, [5]Division of Pharmacogenomics and Personalized Medicine, Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, , Thailand, [6]Division of General Pharmacy Practice, Department of Pharmaceutical Care, College of Pharmacy, Rangsit University, , Thailand, [7]Cancer Research Center of Toulouse, INSERM, UMR-1037, CNRS ERL5294, Paul Sabatier University, , France

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction: DPYD genetic polymorphisms have been widely found to be related to 5-FU-induced toxicities.

Objective: The aim of this study was to establish significant associations between five single nucleotide polymorphisms of DPYD and 5-FU hematological toxicities in Thai colorectal cancer patients.

Methods: The hematological toxicities were analyzed at the first and second cycles of 5-FU administration in all 75 patients who participated in this study. Genotyping was performed using TaqMan real-time PCR.

Results: The patients with homozygous DPYD *9A 85 A>G (GG) had related severe neutropenia since the first cycle of treatment for both Grade 1-4 and Grade 3-4 toxicities ($P = 0.003$, $P < 0.001$ respectively). Upon the second treatment cycle, DPYD *5,1627 A>G was shown to be closely associated with Grade 1-4 toxicity ($P = 0.02$).

Discussion and Conclusion: This suggests that there may be an increased risk of developing 5-FU-induced neutropenia toxicity in Thai colorectal cancer patients carrying the DPYD *9A 85 A>G and DPYD *5,1627 A>G genetic polymorphisms. These findings would make genotyping for DPYD genetic polymorphisms prior to administering 5-FU therapy as part of the standard procedure an appropriate recommendation.

Clearance Factors and Adverse Reactions of Voriconazole in Patients with Hematological Diseases

Hegui Huang[1], Hailing Wang, Pharmacist Yikai Lin, Pharmacist-in-charge Junli Dong, Senior Pharmaceutist Song Hu
[1]Wuhan No.1 Hospital, Wuhan, China, [2]Hubei University of Science and Technology, Xianning, China
Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Objective: To monitor the changes of voriconazole trough concentration (Cmin), and evaluate clearance factors and adverse reactions of voriconazole in patients with hematological diseases, so as to provide a theoretical basis for clinical use of voriconazole. Methods: 136 patients with hematological diseases who used voriconazole in Wuhan NO.1 Hospital from May 2018 to December 2019 were selected. The correlation between C-reactive protein, albumin, creatinine and voriconazole Cmin were analyzed, and the changes of voriconazole Cmin after glucocorticoid treatment was also detected. In addition, stratified analysis was used to analyze risk for voriconazole-related severe adverse events. Results: Among 136 patients, 56.62% of all were male and 43.38% were female. There were positive correlations between voriconazole Cmin and C-reactive protein, creatinine level (r = 0.277, r = 0.2075), while voriconazole Cmin was negatively correlated with albumin level (r = -2.673). Voriconazole Cmin in patients treated with glucocorticoid was decreased significantly (P<0.05). In addition, stratified analysis of voriconazole Cmin showed that, compared with voriconazole Cmin 1.0～5.0 mg/L group, the incidence of adverse reactions of visual impairment in voriconazole Cmin> 5.0 mg/L group was increased ($\chi 2 = 4.318$, $P = 0.038$). Conclusion: The levels of C-reactive protein, albumin and creatinine were closely related to the voriconazole Cmin, which indicated that inflammation and hypoalbuminemia might prevent the clearance of voriconazole in patients with hematological diseases. It is necessary to monitor the voriconazole Cmin of patients with hematological diseases, and adjust the dosage in time to reduce severe adverse events.

Population pharmacokinetics analysis of risperidone long-acting injection using sparse data in patients with schizophrenia

Iva Klarica Domjanović[1], Prof Leon Aarons[2], Dr Kayode Ogungbenro[2], Lana Ganoci[3], Maja Živković[4], Mila Lovrić[5], Nada Božina[6]
[1]Agency for Medicinal Product and Medical Devices of Croatia, , Croatia, [2]Division of Pharmacy and Optometry, University of Manchester, Manchester, United Kingdom , [3]Division of Pharmacogenomics and Therapy Individualization, Department of Laboratory Diagnostics, University Hospital Centre Zagreb, Zagreb, Croatia , [4]Department of Psychiatry, University Hospital Centre Zagreb, Zagreb, Croatia, [5]Analytical Toxicology and Pharmacology Division, Department of Laboratory Diagnostics, University Hospital Centre Zagreb, Zagreb, Croatia, [6]Department of Pharmacology, University of Zagreb School of Medicine, Zagreb, Croatia

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction
A population pharmacokinetic model after bi-weekly administration of long-acting injection (LAI) risperidone was developed with the aim to describe risperidone, 9-hydroxyrisperidone and active moiety (AM, sum of risperidone and 9-hydroxyrisperidone) pharmacokinetics; to estimate pharmacokinetic parameters and associated inter- and intra-individual variability, to evaluate the influence of demographic characteristics (age and gender) and genetic variations (metabolic enzyme CYP2D6 and drug transporters ABCB1 and ABCG2) on risperidone, 9-hydroxyrisperidone and AM pharmacokinetics.

Materials and Methods
Plasma concentration data (two blood samples at steady state) of risperidone, 9-hydroxyrisperidone and AM were obtained from 101 adult (≥18 years) subjects diagnosed with schizophrenia treated with LAI risperidone. The first blood sample was taken at the time of the expected peak exposure after the 4th injection (a.m. on day 5 of week 6) and at trough (end of week 8, before 5th injection). Plasma concentrations were measured by HPLC-DAD method. Genotyping of ABCB1 c.1236C>T, c.2677G>T/A, c.3435C>T, ABCG2 c.421C>A and CYP2D6 xN *3 *4 *5 *6 *10 *41 was performed by TaqMan real-time PCR and long-range PCR; CYP2D6 genotype was translated to metabolic phenotype (poor, intermediate, normal and ultrarapid). Data were analysed using nonlinear mixed-effect model with the Monolix software package. Three separate population pharmacokinetic models for risperidone, 9-hydroxyrisperidone and AM were developed.

Results
Model development was based on sparse data (only two blood samples at steady state) which led to the use of simpler pharmacokinetic models, although it is known that LAI risperidone exhibits a more complex PK profile. The structural model that best described risperidone and AM data was a one-compartment model with first-order absorption and linear elimination. A joint model was developed for metabolite 9-hydroxyrisperidone data and was best described by a one-compartment first-order absorption model for risperidone and two compartment model with linear elimination for 9-hydroxyrisperidone. Due to the sparsity of the data, pharmacokinetic parameters such as volume of distribution (V) and absorption rate constant (ka) needed to be fixed to the literature values, leaving only clearance to be estimated. The standard error for the clearance parameter in all three models, was below 20 % indicating acceptable parameter uncertainty in parameter estimation. Therefore, covariates were analysed against clearance only. The covariate that significantly (based on the change in objective function value of at least 3.84 ($p<0.05$ with one degree of freedom (df), Chi-Square distribution)) affected the pharmacokinetics of risperidone, 9-hydroxyrisperidone and AM was CYP2D6 polymorphism and was left in the final model. A decrease of 47% and 32% in risperidone and AM clearance, respectively, and a decrease of 43% for the clearance from risperidone to 9-hydroxyrisperidone was observed in subjects with decreased enzyme activity (intermediate and poor

metabolizers) when compared to normal and ultrarapid enzyme activity. Goodness of fit plots indicated that the model described the data reasonably well. No other covariates were found to significantly affect risperidone, 9-hydroxyrisperidone and AM pharmacokinetics.

Discussions and Conclusions

Despite having sparse data, the developed population pharmacokinetic models captured the effect of CYP2D6 polymorphism on risperidone metabolism.

Development and evaluation of i-Tracker Ocrelizumab and i-Tracker Anti-Ocrelizumab kits: fast and innovative chemiluminescent assays for the monitoring of patients treated with Ocrelizumab

Georges Khater[1], CEO Simon Davière[1], R&D Director Guillaume Noguier[1], Project Manager Luxziyah Akilian[1], Project Manager Virginie Guilbert[1]
[1]Theradiag, Croissy Beaubourg, France

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Background
Ocrelizumab is a humanized IgG1 monoclonal antibodies directed against CD20-expressing B-cells. This drug is used for the treatment of patients with primary progressive or relapsing forms of multiple sclerosis. Ocrelizumab mediates antibody-dependent cellular cytolysis and complement lysis. Also, Ocrelizumab may induce apoptosis in cross-linking CD20 molecules on the target cell surface. Theradiag has just developed innovative assays for the quantification of Ocrelizumab and Anti-Ocrelizumab antibodies on the fully automated random access i-Track10 chemiluminescent analyzer.

Methods
Analytical performances were assessed with spiked and clinical human serum samples. Ocrelizumab from serum samples was captured by magnetic microparticles coupled with a neutralizing anti-Ocrelizumab antibody and detected with polyclonal antibodies directed against Ocrelizumab conjugated to acridinium ester. Anti-Ocrelizumab antibodies were captured in using Ocrelizumab coupled magnetic microparticles and detected with the use of Ocrelizumab conjugated to acridinium ester. Light emission was linked to the quantity of Ocrelizumab, or anti-Ocrelizumab antibodies, present in the sample.

Results
The dynamic ranges of the assays were 0.5 to 80 µg/mL for Ocrelizumab and 20 to 2000 ng/mL for anti-Ocrelizumab antibodies. Ocrelizumab measurement showed high accuracy (recovery was between 88% and 100%). High precision was reached for both assays (CV were respectively below 6.8% and 7.6% for Ocrelizumab and Anti-Ocrelizumab assays) and no interference was seen with biologic agents.

Conclusion
i-Tracker kits are innovative assays which exhibit fast (time to results < 40min), accurate and reproducible results. i-Tracker kits are valuable tools for the monitoring of patients treated with Ocrelizumab.

Effect of deviations to theoretical sampling times for tacrolimus AUC estimated using Maximum a Posteriori Bayesian Estimation (MAP-BE): a simulation study.

Miss Lea Chiavassa[1], Dr Clément Benoist[1], Dr Marc Labriffe[1,2], Prof Pierre Marquet[1,2], Dr Jean-Baptiste Woillard[1,2]

[1]Inserm U1248 University Of Limoges, Limoges, France, [2]Limoges University Hospital, Limoges, France

Pharmacometrics, Møterom 5, september 25, 2023, 13:00 - 14:30

Introduction: Tacrolimus is an immunosuppressant with a narrow therapeutic index for which therapeutic drug monitoring (TDM) is mandatory. TDM is based on either C0 or AUC but AUC monitoring has been recommended by the last consensus conference. AUC calculation is based on limited sampling strategies backed on population pharmacokinetics models or multiple linear regression equations. The former have been considered more generalizable and flexible in terms of deviation to the theoretical sampling times. The objective of this work was to evaluate by simulation the influence of deviations to theoretical sampling times on tacrolimus AUC calculation estimated using Maximum a Posteriori Bayesian Estimation (MAP-BE).

Material and Methods: Ninety patients were simulated from a literature model (Woillard et al Br J Clin Pharmacol. 2011) in the mrgsolve R package (https://mrgsolve.org/). MAP-BE was applied to each simulated profile based on a 3 samples LSS and the literature model in the MAPBAYR package (Le Louedec et al CPT Pharmacometrics Syst Pharmacol. 2021). The theoretical optimal times being 0, 1 and 3h post dosing, a grid of different combinations of time 0, [30min to 2h] and [2h30min to 4h] yielding to 256 combinations was investigated. The estimated AUC were compared to the true trapezoidal rule AUC for each combination by calculation of the relative mean prediction error (bias) and root mean square error (RMSE). Finally, to achieve reliable reproducibility, the procedure of random simulation was repeated 10 times to obtain for each combination mean and sd values of relative bias and imprecision.

Results: The combination of sampling times associated with the best performance was 0, 1.9h and 3.9h post administration leading to a RMSE of 1.78% (SD= 0.15%) and a bias of 0.04% (SD= 0.2%). The worst performances was for 0, 0.6h and 3.8h associated with a RMSE of 2.2% (SD=1.4%) and a bias of 0.16% (SD = 0.24%). Finally, the median RMSE and bias were 2.0% (SD = 0.16%) and 0.13% (SD=0.20%) respectively.

Discussion and Conclusions: Even if the optimal sampling times were 0, 1.9 and 3.9 hours after administration, we observed that performances were very similar and good whatever the combination of sampling time. Indeed, the difference between the maximum and minimum RMSE was less than 1%, which can be considered as clinically insignificant. Based on these results, deviation of the theoretical sampling times has very little impact on the MAP-BE of tacrolimus.

Real-time, seconds-resolved drug monitoring in solid tissues

Professor Kevin Plaxco[1], Dr. Julian Gearson[1], Ms. Nicole Emmons[1], Ms Lisa Fetter[1], Mr Murat Erdal[1], Professor Carl Kirkpatrick[2], Professor Tod Kippin[1]
[1]University of California, Santa Barbara, Santa Barbara, United States, [2]Monash University, Parkville, Australia

Pharmacometrics, Møterom 5, september 25, 2023, 13:00 - 14:30

Recent advances in biosensors now render it possible to monitor drug concentrations in the body, in real time, and with the same ease and time resolution that we now enjoy in the monitoring of blood sugar. One hurdle remains to be surmounted, however, before this technology can see widespread clinical adaptation: our limited understanding of the relationships between drug concentrations measured in the (easily accessed) subcutaneous interstitial fluid (ISF) and in the plasma, with the latter being the basis of effectively all clinical decision making. Employing electrochemical, aptamer-based sensors we tackled this problem by performing simultaneous, seconds-resolved measurements of multiple drugs in the veins and subcutaneous space of live rats. Using these unprecedented data sets, we have quantitatively modeled drug transport between the plasma and the interstitial fluid, in work that both sheds new light on drug pharmacokinetics in the solid tissues (which are, of course, the site of action of most drugs) and paves the way for wearable, minimally invasive devices supporting continuous, real-time drug monitoring.

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How to predict tacrolimus dose and concentration during voriconazole co-therapy in renal transplantation recipients?

Yichang Zhao, Professor Miao Yan

Immunosuppression 2, Sal D, september 26, 2023, 13:00 - 14:30

Abstract
Objectives
Significant increase in tacrolimus exposure was observed during co-administration with voriconazole, and no population pharmacokinetic model exists for tacrolimus in renal transplant recipients receiving voriconazole. To achieve target tacrolimus concentrations, an optimal dosage regimen is required. This study aims to develop individualized dosing parameters through population pharmacokinetic analysis and simulate tacrolimus concentrations under different dosage regimens.
Methods
We conducted a retrospective study of renal transplant recipients who were hospitalized at the Second Xiangya Hospital of Central South University between January 2016 and March 2021. Subsequently, pharmacokinetic analysis and Monte Carlo simulation were employed for further analysis.
Results
Nineteen eligible patients receiving tacrolimus and voriconazole co-therapy were included in the study. We collected 167 blood samples and developed a one-compartment model with first-order absorption and elimination to describe the pharmacokinetic properties of tacrolimus. The final typical values for tacrolimus elimination rate constant (Ka), apparent volume of distribution (V/F), and apparent oral clearance (CL/F) were 8.39 h-1, 2690 L, and 42.87 L/h, respectively. Key covariates in the final model included voriconazole concentration and serum creatinine. Patients with higher voriconazole concentration had lower tacrolimus CL/F and V/F. In addition, higher serum creatinine levels were associated with lower tacrolimus CL/F.
Conclusions
Our findings suggest that clinicians can predict tacrolimus concentration and estimate optimal tacrolimus dosage based on voriconazole concentration and CREA. The effect of voriconazole concentration on tacrolimus concentration was more significant than serum creatinine. These findings may inform clinical decision-making in the management of tacrolimus and voriconazole therapy in solid organ transplant recipients.

Effect of Voriconazole on Metabolic Activities of CYP3A4/5 Enzymes and Tacrolimus: Based on A Preliminary Exploration and Systematic Analysis

Professor Miao Yan[1]
[1]Second Xiangya Hospital, Central South University, Changsha, China

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Abstract
Objectives
Solid transplant recipients are at increased risk for invasive aspergillosis. Tacrolimus and voriconazole is one of the most common combinations for patients combined with solid transplantation and invasive fungal infections. However, the treatment is difficult due to the interaction between the them. The aim of this study was to investigate the potential drug-drug interaction between tacrolimus and voriconazole by analyzing their inhibitory effects on cytochrome P450 (CYP) enzymes using hepatic microsomes.
Methods
Midazolam and testosterone were used as probe substrates to evaluate individual differences in CYP3A4/5 metabolic activity. A comprehensive interaction analysis was also carried out based on the STITCH database and the DD-Inter system.
Results
When voriconazole concentrations were below 10.00μmol, the inhibition of the CYP3A4/5 enzyme was limited, as shown by the relative percentages of midazolam metabolites ranging from 94.6% to 121%. The median inhibitory concentration for midazolam was calculated to be 379.5μmol, while the value for testosterone was 38.3 μM. The STITCH database and DD-Inter system analysis suggested that tacrolimus and voriconazole share a strong association in liver microsomal metabolism, and CYP3A4/5 and CYP2C19 are the most likely enzymes to interact with them.
Conclusions
The results showed that voriconazole had a significant inhibitory effect on the activity of midazolam and testosterone metabolites, with testosterone being a better probe for detecting CYP3A4/5 activity. The findings may also have broader implications for the management of drug-drug interactions involving other medications that share the same metabolic pathway. Therefore, this study may contribute to improving patient safety and enhancing the quality of care in clinical practice.

A novel automated magnetic bead-based method for the extraction and measurement of plasma voriconazole and meropenem using liquid chromatography tandem mass spectrometry

Ph. D. Xiaoxue Wang[1]
[1]China-Japan Friendship Hospital, 2 Yinghuadongjie Street, Chaoyang, Beijing, China

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Liquid chromatography tandem mass spectrometry (LC-MS/MS) is used routinely in therapeutic drug monitioring, however, automating the sample pretreatment is challenging. We established and evaluated an automated method based on the magnetic bead extraction principle (MBE) to quantify voriconazole and meropenem without centrifugation. The extraction procedure of target analytes contains 4 steps. 1. precipitate protein using organic solvents, 2. add magnetic bead to bind protein, 3. magnetic beads attract magnetic bar, 4. transfer supernatant to LC-MS/MS. The linearity, accuracy, and precision of MBE were evaluated thoroughly. The chromatography peaks of voriconazole and meropenem were symmetrical, without interfering peaks. The linearity of voriconazole and meropenem concentration ranges were 0.62-35.78 µg/mL and 1.05-172.67 µg/mL, with excellent correlation coefficient (r) > 0.99. The accuracy ranged from 90 and 114 % for the two measured drugs, and the within- and between-run precision values were < 9.36% and < 15% for the lower limit of quantification. In conclusion, the automated MBE method for measuring plasma voriconazole and meropenem were successfully developed and applicability demonstrated, and the MBE principle may indicate a new era for LC-MS/MS in clinical application

Analysis of different Voriconazole administration schemes and predictors of its trough concentration and treatment efficacy in patients with liver dysfunction

Yichang Zhao[1,2], Huaiyuan Liu[1,3], Chenlin Xiao[1,2], Jingjing Hou[1,2], Professor Bikui Zhang[1,2], Jiakai Li[1,2], Professor Min Zhang[4], Professor Yongfang Jiang[4], Professor Indy Sandaradura[5,6], Professor Xuansheng Ding[3], Professor Miao Yan[1,2]

[1]Department of Clinical Pharmacy, the Second Xiangya Hospital of Central South University, Changsha, China, [2]Institute of Clinical Pharmacy, Central South University, Changsha, China, [3]School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing, China, [4]Department of Infectious Disease, the Second Xiangya Hospital of Central South University, Changsha, China, [5]School of Medicine, University of Sydney, Sydney, Australia, [6]Centre for Infectious Diseases and Microbiology, Westmead Hospital, Sydney, Australia

Anti-infectives 2 - antibiotics and antifungals, Møterom 4, september 26, 2023, 13:00 - 14:30

This retrospective cohort study aimed to investigate factors influencing the voriconazole trough concentration in patients with liver dysfunction, evaluate the rationality of prior dosing regimens based on total bilirubin, and identify parameters associated with efficacy. A total of 157 patients with liver dysfunction were included, from whom 145 initial and 139 final voriconazole trough concentrations were measured. Of these, 60.5% (95/157) of patients experienced the adjustment of dose or frequency of voriconazole. The initial voriconazole trough concentrations were significantly higher than the final concentrations (mean, 4.47 μg/mL versus 3.90 μg/mL, p=0.0297). CYP2C19 poor metabolizers exhibited significantly higher voriconazole trough concentrations compared to normal or intermediate metabolizers (p=0.0249 and 0.0023, respectively). Furthermore, lymphocyte counts and percentage, platelet, blood urea nitrogen and creatinine five covariates were identified as the factors significantly affecting the voriconazole trough concentration. Binary logistic regression analysis revealed that the lymphocyte percentage significantly affected the efficacy of voriconazole (OR 1.138, 95% CI 1.016 to 1.273). When the lymphocyte percentage was greater than 20.9%, the receiver operating characteristic curve suggested a significant increase in the probability of voriconazole effectiveness. Therefore, total bilirubin-based dosing may be suitable for initial dosing, and the lymphocyte percentage may predict the effectiveness of voriconazole in patients with liver dysfunction. In conclusion, the significant variation in voriconazole trough concentrations observed in patients with liver dysfunction necessitates caution when prescribing this drug. Clinicians should consider the identified factors, particularly CYP2C19 genotype and lymphocyte percentage, when dosing voriconazole in this population.

The antibiotic efficacy of colistin can be increased by therapeutic drug monitoring in patients with multidrug-resistant gram-negative bacterial infections

Dr. Jaeseong Oh[1], Dr. Yunsang Choi[2], Pf. Kyunghoon Lee[3], Pf. Wan Beom Park[4], Pf. Eun Jin Kim[5], Pf. Hong Bin Kim[2], Pf. Eu Suk Kim[2]
[1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea, [2]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea, [3]Department of Laboratory Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea, [4]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [5]Department of Infectious disease, Ajou University School of Medicine, Suwon, Republic of Korea

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction
Colistin use is increasing for treating multidrug-resistant Gram-negative bacterial infections (MDR-GNB), but it is hard to use safely and efficaciously due to its severe adverse drug reactions (e.g., nephrotoxicity). This study aimed to evaluate a therapeutic concentration range of colistin for therapeutic drug monitoring.

Materials and Methods
MDR-GNB patients who are receiving colistin methanesulfonate (CMS), aged more than 18 years, and who are not receiving renal replacement therapy were prospectively recruited. Patients intravenously received CMS doses twice daily according to their individual renal functions. After more than five days of colistin treatment, blood samples were collected to analyse plasma colistin concentration before and two hours after the colistin administration, and pharmacokinetic (PK) parameters including maximum and average plasma concentration (Cmax and Caverage, respectively) and area under the curve (AUC) were calculated by limited sampling method [1]. The emergence of acute kidney injury (AKI) and microbiological evolution were evaluated throughout the study, and the relationship between the colistin PK parameters and the clinical endpoints (i.e., AKI and bacteriological conversion rate) were analysed by a two-sample t-test and logistic regression.

Results
A total of 26 patients were enrolled, and 15 (58%) and 19 (73%) patients among them had AKI and bacteriological conversion, respectively. The PK parameters were not significantly different between the AKI groups. The mean colistin Cmax, Caverage, and AUC in the AKI group were 10.7 mg/L, 7.2. mg/L, and 62.9 mg·h/L, respectively, and those values in the non-AKI group were 10.5 mg/L, 7.2. mg/L, and 62.5 mg mg·h/L, respectively. However, positive exposure-response relationships were observed between the PK parameters and bacteriological conversion rate. The mean colistin Cmax, Caverage, and AUC in the bacteriologically converged group were 11.5 mg/L, 7.6. mg/L, 66.6 mg·h/L, respectively, and those values in non-converged group were 8.2 mg/L, 6.1 mg/L, and 52.3 mg mg·h/L, respectively. (P-values were 0.0435, 0.2789, and 0.0971 for Cmax, Caverage, and AUC, respectively). The optimum cut-off values to discriminate bacteriologically converged groups were 7.6 mg/L, 7.2 mg/L, and 64 mg·h/L, for Cmax, Caverage, and AUC, respectively.

Discussions and Conclusions
In this study the plasma colistin concentration showed a positive relationship with the antibacterial effect of colistin but did not show a clinically meaningful relationship with colistin-induced nephrotoxicity. The therapeutic drug monitoring of colistin may have a limited role in preventing AKI events but can be beneficial for increasing its antibiotic effect during the treatment of MDR-GNB patients.

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Role of early therapeutic drug monitoring in the management of critically ill patients treated with colistin or meropenem.

Dr Sumith K Mathew[1], Dr Binu Susan Mathew[1], Dr Shoma V Rao[1], Ms S Baby Abirami[1], Dr Ratna Prabha[1], Dr Blessed Winston[1], Dr Michael N Neely[2], Dr Abi Manesh[1], Dr Subramani Kandasamy[1], Dr Balaji Veeraraghavan[1], Dr Pamela Christudoss[1]
[1]Christian Medical College, Vellore, Vellore, India, [2]Keck School of Medicine, , United States of America

Anti-infectives 1 - antibiotics and antifungals, Sal B, september 25, 2023, 13:00 - 14:30

Introduction
Pharmacokinetics of colistin and meropenem are altered in critically ill patients, making achievement of therapeutic antibiotic concentrations difficult. Studies exploring clinical outcome in relation to antibiotic exposure over the entire treatment duration are sparse.
Materials and Methods
This prospective study was performed in 45 critically ill patients within 7 days of initiating treatment with colistimethate sodium (CMS) and/or meropenem after a relevant positive culture report. Colistin and meropenem MICs were calculated using the broth microdilution method. Exposure to colistin was measured using a validated LC-MS/MS method and meropenem by a validated HPLC method. The exposure to colistin and meropenem over a period of initial 7 days was predicted using validated colistin and meropenem models in BestDose™ and was communicated to the treating physician. The treating physician decided on the antibiotic dosing regimen. Clinical failure on 7th day of antibiotic treatment was defined as a failure to attain at least 3 of any of the following: WBC count <12000 cells/mm3, afebrile for at least 48 hours, hemodynamically stable without requiring vasopressors, procalcitonin of <0.5 µg/L or reduction by 80%.
Result
Among the 45 patients recruited, 1 was treated with CMS, 22 with CMS plus meropenem, and 22 with meropenem alone. One patient who was initiated with CMS and meropenem was stopped CMS when the culture report came as organism sensitive to meropenem. Among those who were treated with colistin, 13 (59.1%) patients attained the target colistin AUC 24h/MIC of >50 mg.h/L for ≥ 2 days of the first week. Two (4.4%) of 45 patients prescribed combination therapy also attained a trough meropenem concentration >4xMIC, despite MICs in the resistant range. Among those who were primarily treated with meropenem, 15 (65.2%) patients attained trough meropenem concentrations >1xMIC for ≥ 3 days of the first week. 92.9% (26/28) of patients who achieved target antibiotic concentration for colistin or meropenem (at least for ≥ 2 days) attained clinical cure within 7 days of antibiotic treatment compared to 41.2% (7/17) ($p< 0.001$) who did not achieve target antibiotic concentrations. In the 22 who were treated with CMS, 92.3% (12/13) who achieved target colistin concentrations attained cure within 7 days vs. 55.6% (5/9) who did not achieve target colistin concentrations ($p = 0.1$). In those who were primarily treated with meropenem, the proportion of patients who attained cure was 93.3% (14/15) in the target meropenem concentration achieved group vs 25% (2/8) in those who did not achieve target meropenem concentration ($p = 0.002$).
Discussion and conclusion
A significant proportion of critically ill patients did not achieve target antibiotic concentrations for colistin and meropenem with reduced rates of clinical cure at day 7. Relatively large proportion (55.6%) who did not achieve target colistin concentrations attained cure within 7 days may be due to the synergistic effect of co-administered meropenem, despite infection with a carbapenem-resistant organism. Early therapeutic drug monitoring may improve clinical outcome in these patients and should be confirmed in future clinical trials.

Simultaneous Quantification of Trastuzumab and Pertuzumab in Human Serum Using Accurate Mass Spectrometry

Mr Daniel Blake[1], Dr Simon Roberts[2], Dr Eshani Nandita[2]
[1]SCIEX, , United Kingdom, [2]SCIEX, , USA

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction:
Monoclonal antibodies (mAbs) are increasingly being used in combination with other mAbs for cancer and COVID-19 treatments. In breast cancer treatment, trastuzumab and pertuzumab are commonly co-administered to target unique human epidermal growth factor receptor 2 (HER2) epitopes. With the increasing application of mAb co-administration, simple and robust quantification methods are necessary to meet the needs of pharmacokinetic (PK) studies.

Conventional analytical methods involving ligand-binding assays, such as enzyme-linked immunosorbent assays (ELISAs), are employed during PK evaluations due to high sensitivity and sample throughput. However, multiplexing can be a significant challenge for such assays with limited selectivity. In addition to selectivity, sensitivity is also a critical factor because PK studies are often challenged by low sample volumes. Therefore, LC-MS/MS based techniques are being increasingly adopted for PK measurements of combination mAb therapeutics given their enhanced specificity, selectivity and sensitivity. In this study, an immunoaffinity purification workflow with on-bead digestion was employed to simultaneously quantify trastuzumab and pertuzumab in human serum on the ZenoTOF 7600 system.

Methods:

Each sample contained a 10 µL sample of normal human serum, 20 µL of 2 µg/mL SILuMAB, 200 µL of diluted protein A beads and 200 µL of PBS. After samples were shaken for 30 minutes at room temperature, the beads were washed twice with PBS. The beads were resuspended in 150 µL of digestion buffer containing 150 mM ammonium carbonate and 1 mM calcium chloride, and they were denatured at 95°C for 5 minutes. After allowing it to cool to room temperature, 2 µg of trypsin/lys-c was added to each sample and on-bead digestion was performed for 2 hours at 50°C. Digestion was stopped by adding 3 µL of formic acid. Samples were separated from the beads and placed in vials or plates for LC-MS/MS analysis.
Chromatography was performed on a Shimadzu LC-40 X3 system using a Phenomenex Biozen XBC18 (2.1 × 100 mm, 2.6 µm, 100 Å) column. Mobile phase A was 0.1% formic acid in water and mobile phase B was 0.1% formic acid in acetonitrile. The operating flow rate was 0.5 mL/minute. Column temperature was set at 40°C. A 20 µL sample was injected for analysis.

Results:

An LLOQ of 0.15 µg/mL was achieved for trastuzumab and pertuzumab. Matrix interferences in the blank were more than 5x lower than the peak areas in the LLOQ. The overall %CV was <10.1% for trastuzumab and <8.12% for pertuzumab. The overall accuracy was within ±8% of the nominal concentration for trastuzumab. While for pertuzumab, the overall accuracy was within ±12% of the nominal concentration. Strong linearity was achieved with correlation coefficients (r) of >0.996 for both trastuzumab and pertuzumab.

Conclusions:
A highly sensitive method for the quantification of trastuzumab and pertuzumab in human serum using the ZenoTOF 7600 system and on-bead digestion was demonstrated. Using this approach

LLOQs of 0.15 µg/mL were reached for both trastuzumab and pertuzumab in human serum due to the improved MS/MS sampling efficiency offered by the Zeno trap.

Adalimumab and anti-Adalimumab rapid tests - short verification study in a clinical laboratory

Ms Merica Aralica[1], Ms Snjezana Hrabric Vlah[1], Ms Eliza Basic[1], Mr Zoran Bacic[1]
[1]CHC Rijeka, Rijeka, Croatia

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction
Adalimumab (ADL) is an anti-tumor necrosis (TNF) alpha drug for treatment some chronic immune diseases like inflammatory bowel disease or rheumatoid arthritis. Therapeutic drug monitoring by an analyze of ADL and anti-adalimumab antibody (anti-ADL) is an essential part in optimisation patient's therapy. Traditionally, an enzyme linked immunosorbent assay (ELISA) has been used for ADL and anti-ADL analyses in patients' serums, but it has been time consuming in contrast to a rapid test. The objective of presented study was an assessment of analytical performance and clinical agreement of two rapid tests ez-Tracker ADL and ez-Tracker anti-ADL in patients' serums.
Materials and methods
Within-run and between-run precision for ez-Tracker ADL and ez-Tracker anti-ADL (Theradiag, France) were assessed by ez-Tracker commercial control sets; Adalimumab Controls (1 and 2) and anti-Adalimumab Controls (negative and positive), in triplicates for three days using each control level. Method comparison was done in patients' serums between ez-Tracker ADL, a fluorescence immunoassay and LISA-Tracker ADL (Theradiag, France) an ELISA, using Passing-Bablok regression analysis (N=22). The same material was used for an assessment of a clinical agreement between ez-Tracker ADL and LISA-Tracker ADL (N=26) as well as ez-Tracker anti-ADL and LISA-Tracker anti-ADL (N=20), by calculation of Cohen’s κ agreement coefficients.
Results
Within-run and between-run precision of Adalimumab Controls at both levels and anti-Adalimumab positive control were <5% (manufacturer s criteria ranged from 5,5% to 7,9% for all listed controls at associated levels). Anti-Adalimumab negative control (range 0,0-9,99 AU/ml) repeated <0,3 AU/ml result in all nine runs (ez-Tracker anti-ADL measuring range: 0,3-200 AU/ml). Passing-Bablok regression analysis showed y = -0,439362 (95%CI -2,04 to 2,05) + 1,241135 x (95%CI 1,00 to 1,52) and P=0,99. The clinical agreement between ez-Tracker ADL and LISA-Tracker ADL resulted in Cohen’s κ score 0,813 (95%CI 0,621 to 1,000), while between Tracker anti-ADL and LISA-Tracker anti-ADL, Cohen’s κ score was 0,667 (95%CI 0,339 to 0,995).

Conclusion
Presented results revealed that both rapid tests showed an excellent within-run and between-run precision. An exception was ez-Tracker anti-ADL in negative range (<10 AU/ml) due to results below measurement range in all runs. It made impossible an estimation of ez-Tracker anti-ADL within-run and between-run precision at level below 10 AU/ml. Method comparison and clinical agreement between ez-Tracker ADL and LISA-Tracker ADL showed acceptable results, making ez-Tracker ADL interchangeable to LISA-Tracker ADL. The clinical agreement between ez-Tracker anti-ADL and LISA-Tracker anti-ADL was less superb but still good. A small set of anti-ADL samples with results between 10 AU/ml to 200 AU/ml prevented method comparison analysis between two anti-ADL tests resulting in partial analysis of ez-Tracker anti-ADL analytical performance.
In conclusion, both ez-Tracker tests are promising alternative to the ELISA testing in future, but some improvement is needed regarding negative control for anti-ADL.

Minimal impact of antiretroviral boosters (cobicistat, ritonavir) on the pharmacokinetics of tenofovir disoproxil fumarate

Dr François Parant[1], Dr Aurélien Millet[1], Dr Marie-Claude Gagnieu[1]
[1]Centre de Biologie Sud - LBMMS, Lyon, France

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction Data from the meta-analysis by Hill et al. (2018) suggest that tenofovir disoproxil fumarate (TDF) plus ritonavir (RTV) or cobicistat (COBI) boosted antiretroviral (ARV) therapy is associated with higher risks of bone and kidney adverse events compared to tenofovir alafénamide (TAF). In contrast, when RTV and COBI are not combined, there are only marginal differences in tolerance (1). The authors attribute these results to plasma overexposure to tenofovir (TNF) when RTV or COBI are combined. However, the data from the literature are quite contradictory. The objective of this study is to carry out a pharmacokinetic modeling of TNF by population approach based on data from Therapeutic Drug Monitoring (TDM) and to identify covariates that might explain variability in TNF exposure.

Materials and Methods Inclusion criteria: People Living with HIV (PLHIV) treated with TDF/emtricitabine 300/200 mg; over 16 yrs. of age; TNF concentrations available from TDM; date and time of last dose, patient's weight and GFR provided. Exclusion criteria: pregnant women, dialysis patients, non-compliant patients. A total of 787 patients (530/257 M/F) with a median age of 47 yrs. (IQR: 39-55) were included. The number of samples collected (=observations) from each occasion ranged from 1 to 4 (mean: 1.2). The number of occasions per PLHIV ranged between 1 and 17 (mean: 1.4), and the total number of occasions was 1136. The modeling was carried out using the Monolix 2021R2 software, according to a 2-compartment model with linear absorption and elimination (2). The following covariates were tested on the model: age, weight, GFR, phosphoremia, boosted regiment and other treatments likely to impact the clearance of TNF (e.g. ledipasvir, rifampicin).

Results As expected, renal function has a strong impact on the TNF apparent clearance (Cl/F). Clearance also decreases with age while it increases with weight. Ledipasvir lowers the Cl/F of TNF quite markedly with an increase in the AUC of TNF of +57% (47-68%). Boosted ARV treatments associated with TNF have a lower impact with an increase in AUC of TNF of +9% (5-12%), and +17% (11-24%), for RTV and COBI, respectively. The other associated treatments tested, in particular rifampicin and daclatasvir, have no impact on the Cl/F of TNF.

Conclusion These results from routine TDM confirm the real but fairly weak impact of boosted ARV treatments on plasma TNF exposure levels. Does this low plasma overexposure alone explain the lower tolerance of TNF when it is associated with a boost? Would a dose reduction be necessary as suggested by Hill et al.?

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Practical utility evaluation of a fully-automated method for quantifying 12 oral small molecule anticancer drugs

Practical utility evaluation of a fully-automated method for quantifying 12 oral small molecule anticancer drugs Reiko Ando Makihara[1,6], Practical utility evaluation of a fully-automated method for quantifying 12 oral small molecule anticancer drugs Yuki Katsuya[2], Practical utility evaluation of a fully-automated method for quantifying 12 oral small molecule anticancer drugs Makoto Maeda[1], Practical utility evaluation of a fully-automated method for quantifying 12 oral small molecule anticancer drugs Daisuke Amenomiya[1], Practical utility evaluation of a fully-automated method for quantifying 12 oral small molecule anticancer drugs Kohei Yoshikawa[7], Practical utility evaluation of a fully-automated method for quantifying 12 oral small molecule anticancer drugs Eishi Imoto[7], Practical utility evaluation of a fully-automated method for quantifying 12 oral small molecule anticancer drugs Daisuke Kawakami[7], Practical utility evaluation of a fully-automated method for quantifying 12 oral small molecule anticancer drugs Yuki Kojima[3,6], Practical utility evaluation of a fully-automated method for quantifying 12 oral small molecule anticancer drugs Tatsuya Yoshida[2,4], Practical utility evaluation of a fully-automated method for quantifying 12 oral small molecule anticancer drugs Takafumi Koyama[2,6], Practical utility evaluation of a fully-automated method for quantifying 12 oral small molecule anticancer drugs Akiko Kubo[1], Practical utility evaluation of a fully-automated method for quantifying 12 oral small molecule anticancer drugs Daisuke Watabe[1], Practical utility evaluation of a fully-automated method for quantifying 12 oral small molecule anticancer drugs Yoshimasa Saito[1], Practical utility evaluation of a fully-automated method for quantifying 12 oral small molecule anticancer drugs Toru Akagi[1], Practical utility evaluation of a fully-automated method for quantifying 12 oral small molecule anticancer drugs Ken Kato[5,6], Practical utility evaluation of a fully-automated method for quantifying 12 oral small molecule anticancer drugs Noboru Yamamoto[2], Practical utility evaluation of a fully-automated method for quantifying 12 oral small molecule anticancer drugs Hironobu Hashimoto[1]
[1]Department of Pharmacy, National Cancer Center Hospital, Tokyo, Japan, [2]Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan, [3]Department of Medical Oncology, National Cancer Center Hospital, Tokyo, Japan, [4]Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan, [5]Department of Head and Neck, Esophageal Medical Oncology / Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan, [6]Translational Research Specimen Control Section, National Cancer Center Hospital, Tokyo, Japan, [7]SHIMADZU CORPORATION, Kyoto, Japan

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction

Personalization of oral small molecule anticancer drug dosages based on therapeutic drug monitoring (TDM) has the potential to significantly improve the effectiveness of treatment by maximizing drug efficacy and minimize toxicity. However, TDM has not been widely implemented in clinical practice. This is partly due to the complex measurement system and the associated turnaround time (TAT).

Materials and Methods

We have developed and validated a fully-automated method for quantifying 12 small molecule anticancer drug currently used (abemaciclib, cabozantinib, imatinib, lenvatinib, lorlatinib, olaparib, osimertinib, palbociclib, pazopanib, regorafenib and its metabolites, sunitinib and its metabolite) in human plasma using LC-MS/MS for TDM in clinical practice. Extraction procedures, including protein precipitation, extraction and collected extract, were performed automatically by the automated sample preparation system CLAM-2030 connected to the LC/MS system which consisted of a Nexera HPLC and a LCMS-8050. The primary endpoint of the study was the feasibility of TAT of TDM within 90 minutes. The first TAT of TDM was evaluated in each patient, and estimated sample size was 65 patients. A calibration curve was prepared the day before or on the day of blood collection, and the quality control samples were used to confirm the results on the day of collection. The study protocol

was approved by our institutional review board and informed consent was obtained from all patients.

Results

Before beginning this clinical study, a validation study was first conducted. The analysis time of the method was 8.5 minutes per run, and all analytes eluted within 3.0–6.0 minutes. The method was linear over each range, with correlation coefficient values >0.99. The intra-day and inter-day precision were below 15%, and accuracy were within ± 20% of the nominal concentrations, respectively. These results met the criteria of the US Food and Drug Administration validation guidelines. Until March 31st, fifty patients have been registered in the feasibility study, and forty-nine patients excluding one without blood sample were analyzed. The median age was 64 (34–88) years; 18 were male and 32 were female. Of these, 15 were treated with osimertinib, 9 with abemaciclib, 8 with imatinib, and 17 with other treatments. In a total of 49 patients, 94% were able to return results within 90 minutes, and the mean of the time between sampling and results was 52 (17–156) minutes.

Discussions and Conclusion

This real-time TDM using fully-automated LC-MS/MS method for simultaneous quantification of plasma concentrations of 12 small molecule anticancer drug seems feasible in clinical practice. Having solved the problems of complexity and TAT, we are now considering a study to verify whether TDM is effective in clinical practice using the method developed in this study.

How to implement vancomycin model-informed precision dosing in clinical practice?

Ms Maria Swartling[1], Anna-Karin Hamberg[2], Mia Furebring[3], Thomas Tängdén[3], Elisabet I Nielsen[1]
[1]Department of Pharmacy, Uppsala University, Uppsala, Sweden, [2]Department of Clinical Chemistry and Pharmacology, Uppsala University Hospital, Uppsala, Sweden, [3]Department of Medical Sciences, Infection Medicine, Uppsala University, Uppsala, Sweden

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction
For vancomycin, model-informed precision dosing (MIPD) has been shown to improve the pharmacokinetic/pharmacodynamic target attainment. However, the dissemination of MIPD into clinical practice is slow. The aim of this project was to develop an implementation strategy for optimised dosing of vancomycin using MIPD in a Swedish university hospital and select process indicators for its evaluation.

Methods
Guided by the UK Medical Research Council's framework for developing and evaluating complex interventions (1), an intervention with an associated implementation plan was developed for a Swedish university hospital.

Supportive documents and educational material were developed in collaboration with representatives from target professions.

Using the Implementation Research Logic Model (2), intervention components and implementation activities were connected with mechanisms of actions for implementation strategies and expected outcomes. Based on this, process indicators were identified, prioritised and selected for the evaluation.

Results
The resulting intervention included a new clinical routine for AUC-guided vancomycin MIPD and a team-based workflow with defined ways of communication and responsibilities. The implementation strategies were 1) tailoring of the clinical routine at ward level 2) written instructions and a peer support function as part of the workflow 3) staff training to improve determinants for successful implementation at health-care provider level.

Implementation was initiated at the Blood and Tumour division, Uppsala University Hospital in January 2023. A local written clinical routine for AUC-guided vancomycin dosing was constructed in collaboration with representatives from the selected wards. For nurses, an instruction for accurate documentation of dose administration and TDM sampling was written and an educational film was produced. This was combined into a 15-minute educational package for in-service training held at six occasions. For physicians and clinical pharmacists, 45-minute educational sessions were held at four occasions. For clinical pharmacologists and pharmacists, a written instruction for MIPD was produced, individual case-based mentoring was provided and MIPD rounds were introduced. AUC-guided MIPD of vancomycin according to the new routine commenced February 27 2023.

Expected outcomes and selected process indicators for evaluation include: acceptability / staff opinions on intervention and implementation; timeliness / median and range of time from sampling to reported AUC; feasibility / pharmacist time consumption per TDM sample; fidelity / proportion of TDM samples with TDM report, proportion of doses changed according to dose suggestion in TDM report, proportion of dose decisions with pharmacist support.

Discussion and conclusion
An implementation process for introducing vancomycin MIPD in clinical practice and related indicators for its evaluation was developed. This framework can be used as guidance for other institutions with similar context wishing to initiate and evaluate MIPD of vancomycin in a clinical setting.

During the implementation process, the intervention context prerequisite “available MIPD expertise” was identified as a future barrier to large-scale implementation on a national level. A network to increase knowledge about MIPD applied in clinical practice is warranted.

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Development and evaluation of i-Tracker Natalizumab and i-Tracker Anti-Natalizumab kits: fast and innovative chemiluminescent assays for the monitoring of patients treated with Natalizumab

Georges Khater[1], CEO Simon Davière[1], R&D Director Guillaume Nogier[1], Project Manager Amandine Puig[1], Project Manager Christophe Montaillier[1]
[1]Theradiag, Croissy Beaubourg, France

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Background
Natalizumab is a humanized IgG4 monoclonal antibody directed against human α4 integrin. This drug is used for the treatment of patients with relapsing forms of multiple sclerosis and, also, for the treatment of Crohn's disease. Natalizumab blocks the interaction of α4 integrin with vascular cell adhesion molecule (VCAM-1) to prevent the adherence and migration of inflammatory immune cells across the intestinal and blood-brain barrier. Theradiag has just developed innovative assays for the quantification of Natalizumab and Anti-Natalizumab antibodies on the fully automated random access i-Track10 chemiluminescent analyzer.

Methods
Analytical performances were assessed with spiked and clinical human serum samples. Natalizumab from serum samples was captured by magnetic microparticles coupled with a neutralizing anti-Natalizumab antibody and detected with polyclonal antibodies directed against Natalizumab conjugated to acridinium ester. Anti-Natalizumab antibodies were captured in using Natalizumab coupled magnetic microparticles and detected with the use of Natalizumab conjugated to acridinium ester. Light emission was linked to the quantity of Natalizumab, or anti-Natalizumab antibodies, present in the sample.

Results
The dynamic ranges of the assays were 0.5 to 60 µg/mL for Natalizumab and 20 to 1000 ng/mL for anti-Natalizumab antibodies. Natalizumab measurement showed high accuracy (recovery was between 80% and 120%). High precision was reached for both assays (CV were <20%) and no interference was seen with biologic agents.

Conclusion
i-Tracker kits are innovative assays which exhibit fast (time to results < 40min), accurate and reproducible results. i-Tracker kits are valuable tools for the monitoring of patients treated with Natalizumab.

Simultaneous Determination of Different Classes of β-lactam Antibiotics in Human Plasma

S Uhlen, C Marzullo, A Morla
[1]SCIEX, , United Kingdom

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Simultaneous Determination of Different Classes of β-lactam Antibiotics in Human Plasma

β-Lactam are among the most widely used class of drugs for the treatment of bacterial infections in humans. Most β-lactam antibiotics work by inhibiting cell wall biosynthesis in the bacterial organism. Bacteria often develop resistance to these antibiotics by synthesizing a β-lactamase, an enzyme that attacks the β-lactam ring common to this class of antibiotic. To overcome this resistance, β-lactam antibiotics can be given with β-lactamase inhibitors such as clavulanic acid. The antibacterial characteristics the drugs display are dependent on both the concentration of drug in relation to the minimum inhibitory concentration (MIC) and the time that this exposure is maintained. Therefore, monitoring their concentrations in plasma is of high importance.

In this study, a fast LC-MS/MS method with a simple sample preparation on the QTRAP 4500 system is described for the quantitative analysis of nine β-lactams antibiotics, amoxicillin (AMO), cloxacillin (CLO), piperacillin (PIP), cephazolin (CEP), cefotaxime (CEFO), ceftazidime (CEFT) and cefepime (CEFE), imipenem (IMI) and meropenem (MER).

Methods:
A 100 µL aliquot of each sample, calibrator or QC was spiked with 10 µL of internal standard mix at 100 µg/mL. Protein precipitation was carried out by the addition of 200 µL of methanol containing 0.1% formic acid. Following vortex mixing, the samples were centrifuged for 10 minutes before the supernatant was transferred to autosampler vials for injection. Chromatographic separation was accomplished using a Phenomenex Kinetex Biphenyl column (100 x 2.1 mm, 2.6 µm). Water with 0.1% formic acid (A) and methanol with 0.1% formic acid (B) were used as mobile phase solvents. A 1 µL aliquot of the sample was injected into the UHPLC system. MS/MS detection was performed using the SCIEX QTRAP 4500 system equipped with Turbo V ion source using electrospray ionization, operating in positive mode. Multiple reaction monitoring (MRM) mode was employed, using two specific transitions of each analyte.

Results:
Calibration curves over the concentration ranges were between 1 and 150 µg/mL for all analytes except imipenem (0.05 to 7.5 µg/mL) and meropenem (0.1 to 15 µg/mL). Curves were generated using a 1/x weighted linear regression of the peak-area ratios of the antibiotic to corresponding internal standard. Regression coefficients of all calibration curves were greater than 0.99 with back-calculated concentrations of the calibration samples within ±15% (±20% at LLOQ) of the nominal concentrations. The recorded accuracy and precision were within European Medicines Agency guidelines. The application of this assay for nine β-lactams antibiotics was then used to analyze plasma samples from the Hospital of Mulhouse Antibiotic Therapeutic Drug Monitoring (TDM) program and compared to alternative methods for the analysis of these compounds.

Conclusions:
The QTRAP 4500 system was used for the quantitative analysis of nine β-lactams antibiotics, amoxicillin (AMO), cloxacillin (CLO), piperacillin (PIP), cephazolin (CEP), cefotaxime (CEFO), ceftazidime (CEFT) and cefepime (CEFE), imipenem (IMI) and meropenem (MER). Sensitivity was shown to be 1 µg/mL for all analytes except imipenem (0.05 µg/mL) and meropenem (0.1 µg/mL) in plasma.

In-depth evaluation of automated non-contact reflectance-based hematocrit prediction of dried blood spotsp

Laura Boffel[1], PharmD Liesl Heughebaert[1], Dr Stijn Lambrecht[2], Dr Marc Luginbühl[3], Prof. Dr. Christophe Stove[1]
[1]Laboratory of Toxicology, Ghent University, Ghent, Belgium, [2]Laboratory of Clinical Chemistry and Hematology, Ghent University Hospital, Ghent, Belgium, [3]CAMAG, Muttenz, Switzerland
Alternative Sampling Strategies 1, Møterom 1, september 25, 2023, 13:00 - 14:30

INTRODUCTION: Dried blood spot(s) (DBS) microsampling has increasingly attracted interest as a patient-centric alternative to conventional blood collection. Despite the many advantages associated with DBS sampling, its widespread use in clinical practice is still hampered, which is mainly caused by the hematocrit (Hct) effect. Different approaches to cope with this issue have been developed, amongst which the Hct prediction of DBS using ultraviolet-visible (UV-Vis) spectroscopy. Recently, a UV-Vis-based Hct prediction module has been incorporated into the automated CAMAG® DBS-MS 500 HCT system. However, although a proof-of-principle yielded promising results, there is no formal in-depth evaluation of the performance of this module. Hence, it remained to be established to what extent automated Hct prediction of DBS via this module can universally be applied and generates acceptable results.
MATERIALS AND METHODS: Using calibrators (n = 95) and quality control (QC) samples (n = 42), both generated from authentic patient samples, we set up and validated a calibration model and evaluated whether this could serve as a 'generic' calibration model for different, independent Hct prediction modules. Also, the influence on the Hct prediction of different storage conditions and DBS-related variables, including spotted blood volume, non-standard 'spotting variables' and filter paper type, were evaluated using a subset of the QC samples. Finally, the method was applied on an independent set of venous DBS (n = 48) prepared from patient samples in the context of therapeutic drug monitoring (TDM) of tacrolimus.
RESULTS: A quadratic calibration curve with $1/x^2$ weighting was established. The bias, intra-day and total precision for 8 different cohorts reflecting Hct sub-ranges from 0.157 to 0.537 L/L were below 0.025 L/L, 2.2% and 2.7%, respectively. Additionally, storage (freeze-thawing, storage at room temperature and 60 °C), some non-standard DBS application techniques and filter paper type did not affect the Hct prediction. Moreover, a lab-lab comparison of the performance of the Hct module of two independently operated instruments demonstrated that the validated model can be used as a 'generic' calibration model. Finally, application of the method to venous DBS prepared from patient samples in the context of TDM of tacrolimus revealed a good concordance between the actual (i.e. Sysmex-based) and UV-Vis-based predicted Hct, with a mean bias of -0.003 L/L (95% CI -0.014 to 0.008 L/L) and with > 80% of the samples within the pre-set acceptance limit of +/-0.50 L/L.
CONCLUSION: We extensively and successfully validated a 'generic' calibration model for the automated UV-Vis-based Hct prediction module incorporated into the CAMAG DBS-MS 500 HCT system. This automated non-contact Hct prediction approach allows to correct for the Hct-based bias observed in partial-punch DBS analysis, with the substantial advantage that a fully automated set-up eliminated any hands-on time, increasing the potential of DBS to be implemented in routine clinical practice.

A plasmatic score using a miRNA signature and CXCL-10 for accurate prediction and diagnosis of liver allograft rejection

Dr Olga Millán[1], Dr Pablo Ruiz[2], Dr Judit Julian[3,5], Dr Yiliam Funfora[4], Dr Gonzalo Crespo[2], Dr Jordi Colmenero[2], Dr Miquel Navasa[2], Prof Mercè Brunet[5]
[1]Liver and Digestive Diseases Networking Biomedical Research Centre (CIBERehd), Pharmacology and Toxicology, Biomedical Diagnostic Center (CDB), Hospital Clínic Barcelona, IDIBAPS, University of Barcelona, Barcelona, Spain, , Spain, [2]Liver Transplant Unit, Hospital Clinic Barcelona, IDIBAPS, CIBERehd, University of Barcelona, Barcelona, Spain, , Spain, [3]Biochemistry and Molecular Genetics, Biomedical Diagnostic Center, Hospital Clínic Barcelona, Barcelona, Spain, , Spain, [4]Department of General and Digestive Surgery, Hospital Clínic Barcelona, IDIBAPS, CIBERehd, University of Barcelona, Barcelona, Spain, , , [5]Pharmacology and Toxicology, Biomedical Diagnostic Center (CDB), Hospital Clínic Barcelona, IDIBAPS, CIBERehd, University of Barcelona, Barcelona, Spain, ,

Immunosuppression 1, Sal D, september 25, 2023, 13:00 - 14:30

Introduction: The diagnosis of rejection in liver transplantation (LT) requires a liver biopsy (LB) when abnormal liver function tests (LFTs) are observed. The use of noninvasive biomarkers may avoid the need for LB and could promote a more efficient immunosuppressive therapy adjustment. Plasma microRNA (miRNA) expression and certain chemokines have been proposed as potential biomarkers of rejection. The aims of this study were: 1) to confirm the predictive and diagnostic capacity of plasmatic expression of miR-155-5p, miR-181a-5p, miR-122-5p and CXCL-10 for assessing T-cell mediated rejection (TCMR) risk; 2) to develop a score based on a panel of noninvasive biomarkers to predict graft rejection and graft dysfunction risk; and 3) to validate this score in a separate cohort.
Methods: A prospective, observational study was conducted with a cohort of 79 patients followed during the first year after LT. Tacrolimus trough concentrations were determined by Tacrolimus-CMIA-Architect from Abbot at the 1st week, on the 15th day, and at the 1st, 2nd, 3rd, 6th, 9th and 12th months after LT. Plasma samples were collected at same time points for the analysis of miR-155-5p, miR-122-5p and miR-181a-5p and the CXCL-10 chemokine. Patients with LFTs abnormalities were submitted to a LB to rule out rejection, assessing previous and concurrent expression of the biomarkers to evaluate their predictive and diagnostic ability. Information from 86 patients included in a previous study was collected and used as a validation cohort.
Results: A total of 24 rejection episodes were diagnosed in 22 patients (27.8%). Only at day 15th tacrolimus trough levels were significantly lower in the patients with rejection (6.60 vs. 4.75 ng/ml, p=0.008).The plasma CXCL-10 concentration and the expression of the three miRNAs were significantly elevated prior to and at the moment of the diagnosis of rejection. These and other significantly altered variables were used to develop a logistic model for rejection prediction and diagnosis. The final model included CXCL-10, miR-155-5p and miR-181a-5p. The area under the ROC curve (AUROC) for rejection prediction was 0.975 (79.6% sensitivity, 99.1% specificity, 90,7% PPV; 97.7% NPV; 97.1% correctly classified) and 0.99 for diagnosis (87.5% sensitivity, 99.5% specificity, 91.3% PPV; 99.3% NPV; 98.9% correctly classified). In the validation cohort (n=86; 14 rejections), the same cut-off points were used obtaining AUROCs for rejection prediction and diagnosis of 0.89 and 0.92 respectively. In patients with graft dysfunction in both cohorts (37 with rejection and 19 with other findings), the score could discriminate those with rejection regarding other causes with an AUROC of 0.98 (97.3% sensitivity, 94.1%specificity).
Conclusions: These results strongly suggest that the clinical implementation of the monitoring of this noninvasive plasmatic score, based on CXCL-10 and miR-155-5p and miR-181a-5p, may allow the prediction and diagnosis of rejection and identify patients with graft dysfunction due to rejection, helping with a more efficient guide for immunosuppressive therapy adjustment and improving the quality of life of patients. This finding warrants the development of prospective biomarker-guided clinical trials.

Population pharmacokinetics modeling and dosing simulation for vancomycin in young children with congenital heart disease

B.S. Yuko Shimamoto[1], Ph.D. Keizo Fukushima[2], Ph.D. Tomoyuki Mizuno[2], M.D., Ph.D. Hajime Ichikawa[3], M.D., Ph.D. Kenichi Kurosaki[4], Ph.D. Shinichiro Maeda[5], Ph.D. Masahiro Okuda[5]
[1]Department of Pharmacy, National Cerebral and Cardiovascular Center, Osaka, Japan, [2]Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, USA, [3]Department of Pediatric Cardiovascular Surgery, National Cerebral and Cardiovascular Center, Osaka, Japan, [4] Department of Pediatric Cardiology, National Cerebral and Cardiovascular Center, Osaka, Japan, [5]Department of Hospital Pharmacy, Graduate School of Medicine, Osaka University, Osaka, Japan

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

INTRODUCTION:
Providing safe and effective drug therapy to infants and young children requires consideration of growth and development on the PK/PD. Congenital heart disease (CHD) is the most common congenital anomaly, affecting approximately 1 % of liveborn children. Pediatric patients with CHD are required multiple staged surgery depending on age and disease condition in complex cases. The pediatric vancomycin (VCM) dosage recommended by The Infectious Diseases Society of America (IDSA) guidelines is 60-80 mg/kg/day when targeting an AUC/MIC ratio of 400-600. However, this dosage frequently results in overexposure in pediatric patients undergoing staged operations for CHD in our institution. This study aimed to determine an appropriate VCM dosing regimen for young children with CHD through population PK modeling and simulations.

MATERIALS AND METHODS:
A total of 1,254 VCM serum concentrations from postoperative 152 patients (3 days - 13 years old) were available for analysis. eGFR was estimated using the updated Schwartz equation [Zhang et al. Clin Pharmacol Ther 2021]. Population PK analysis was performed with Phoenix NLME 8.3. The effect of growth and maturation on VCM clearance was described by allometrically scaled body weight and a sigmoidal maturation function using postmenstrual age (PMA), respectively. The developed PK model was used for simulation analyses to evaluate the achievement of a target of 400 ≤ AUC/MIC ≤ 600 to determine optimal dosing regimens.

RESULTS:
Body weight and height were < 5 percentiles of the CDC growth charts in 74% and 64% of the patients in this study. Median of observed VCM dosage was 13.2 mg/kg every 12 hours. The eGFR, body weight, and PMA were identified as significant covariates on clearance and the population mean estimates of VCM clearance was 4.88 L/h/70 kg. The post hoc clearance was lower than the previously reported value; 33% lower in age ≤ 1 year and 40% lower in age 1 year < age ≤ 2 years [Colin et al. Clin Pharmacokinet 2019], indicating the delayed maturation of renal function. The identified VCM doses to reach 400 ≤ AUC/MIC ≤ 600 for age ≤ 3 months (median eGFR 40 mL/min/1.73m2) and 3 months < age ≤ 3 years (median eGFR 60 mL/min/1.73m2) were 25 mg/kg/day and 35 mg/kg/day, respectively.

DISCUSSIONS AND CONCLUSIONS:
In this study, VCM PK model for pediatric patients with CHD was established and age- and renal function-appropriate VCM dosing regimen was determined to address delayed renal maturation observed in CHD children.
The observed delayed maturation in VCM clearance is possibly due to cyanosis and low cardiac output. The model-informed simulations identified the lower VCM doses than the current standard dosage and the developed VCM dosing regimen may provide safe and effective antibiotic therapy for this high-risk population.

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THERAPEUTIC DRUG MONITORING OF MYCOPHENOLIC ACID AND TACROLIMUS BASED ON VOLUMETRIC-ABSORPTIVE MICROSAMPLING (VAMS) AS A RELIABLE TOOL FOR ADHERENCE MONITORING IN RENAL PEDIATRIC TRANSPLANT RECIPIENTS - SINGLE-CENTER, OPEN-LABEL, RANDOMIZED CONTROLLED TRIAL

MSc MPharm Arkadiusz Kocur[1,2], PhD MD Jacek Rubik[3], MSc Agnieszka Czajkowska[2], PhD PharmD Tomasz Pawiński[1]

[1]Medical University of Warsaw Department of Drug Chemistry, Warsaw, Poland, [2]Department of Biochemistry, Radioimmunology, and Experimental Medicine, Pharmacokinetics Laboratory, The Children's Memorial Health Institute, Warsaw , Poland, [3]Department of Nephrology, Kidney Transplantation, and Arterial Hypertension, The Children's Memorial Health Institute, Warsaw , Poland

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

1. Introduction

Incompatibility with treatment regimens is a complex problem, especially in adolescents and children after transplantation. Long-term transplant outcomes in adolescents are disappointing despite excellent one-year graft survival. The non-use of immunosuppressive drugs is one of the most critical factors contributing to graft loss (chronic and acute rejection episodes). The primary risks of non-compliance are low-income family support and poor mental functioning of the child. Secondarily, the side effects of using immunosuppressive drugs often influence it. Lifelong immunosuppressive therapy is required for all transplant patients to avoid chronic or acute rejection episodes. More significant variability in TAC, MPA, and PRE concentrations (in the case of non-compliance) is associated with acute rejection, reduced graft survival, and increased therapy costs. The variability of TAC and MPA trough concentrations is an easy tool that may be used to assess adherence. This is defined as the fluctuating C0 level at specific time intervals without changing the dose.

2. Materials and Methods

The study is a one-center, prospective, randomized, open-label study concerning the utility of VAMS accomplished by liquid chromatography combined with triple quadrupole mass spectrometry for TDM of TAC and MPA in pediatric transplant recipients treated at Children's Memorial Health Institute in Warsaw. The study will be performed with 60 patients between 2 and 18 years of age treated with TAC and MPA (mycophenolate mofetil prodrug of MPA), with drug dosage guided by therapeutic drug monitoring (TDM). Patients were randomly divided into two groups depending on how the sample was collected: standard venous blood sampling and new technology-based VAMS. Blood samples from patients in the reference group (traditional sampling) were determined independently using the reference LC-MS/MS and routine diagnostic methods. Simultaneous analogous samples from patients in the tested group (self-management) were collected using VAMS and determined similarly. Analysis of trough concentrations (C0) of TAC and MPA was simultaneously performed using an LC system with triple quadrupole mass spectrometry with positive mode electrospray ionization (ESI+). Intra-individual variability was calculated using different statistical methods: standard deviation (SD) and coefficient of variation (CV). Additionally, adherence to the therapy was evaluated based on a questionnaire investigation.

3. Results

In the case of the included patients, the CV of TAC and MPA concentration was < 40% (using six concentrations). More than 90% of the patients during the 6-month observation period were adherent to immunosuppressive therapy. All participants were included in the trial, and their parents were satisfied with the microsampling method.

4. Discussions and Conclusions

The results from home-based self-sampling TDM of TAC and MPA could be used for pharmacotherapy optimization, including adherence evaluation. Introducing the VAMS as a sampling strategy in ordinary questionnaire evaluation could significantly increase adherence in pediatric patients after renal transplantation.

Evaluation of the drug-drug interaction between posaconazole and tacrolimus in the early period aferr renal transplantation

Dr. Nan Hu[1], Mrs Liying Wang[1], Mr Rong Chen[1]
[1]The Third Affiliated Hospital of Soochow University, Changzhou, China

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Objective Tacrolimus, one of the calcineurin inhibitors, is a commonly used immunosuppressive drug in patients with renal transplantation. Tacrolimus is mainly metabolized by CYP3A4 in liver. Antifungal drug posaconazole is a potent CYP3A4 inhibitor drug, and could exhibit drug-drug interaction when combinated with some CYP3A4 substrates, such as tacrolimus. However, the drug-drug interaction has great individual differences, which is also unpredictable. The drug instruction of tacrolimus suggest that it is necessary to reduce the dose of tacrolimus when used in combination with posaconazole, but it does not provide individualized medication guidance. Therefore, this study is intended to investigate the drug-drug interaction between posaconazole and tacrolimus in renal transplantation patients at early stage and the influencing factors of individual differences. Methods A total of 32 hospitalized patients who received posaconazole for treatment or prevention of fungal infection after renal transplantation in our hospital were enrolled in this study. Medication information and blood concentration data of tacrolimus and posaconazole were collected during the period. The polymorphism of CYP3A5*3, ABCB1 3435, ABCB1 1236 and POR*28 genes were detected. Results The results showed that tacrolimus concentration (C) significantly increased after posaconazole combined with tacrolimus (7.45±2.85 vs 9.58±2.64 ng/mL, P<0.05). The dose (D) was significantly decreased (5.46±1.95 vs 3.09±1.83 mg/kg/d, P<0.01) and the concentration/dose ratio (C/D) was significantly increased (90.95±43.19 vs 249.58±134.01 ng·kg/mL/mg/d, P<0.01). The value of C, D and C/D were 1.29, 0.57 and 2.74 times of those before combination, respectively. The drug-drug interactions between tacrolimus and posaconazole were significant and individual differences were large. The correlation analysis between genotype and the ratio of C/D before and after posaconazole treatment (Δ C/D) was conducted. It was showed that ABCB1 3435 was significantly correlated with ΔC/D, and the ΔC/D of ABCB13435 CC genotype was significantly lower than that of CT/TT genotype. The other loci, including CYP3A5*3, ABCB11236 and POR*28, had no significant correlation with ΔC/D. In addition, the posaconazole concentration was 0.49±0.28 ug/mL, which was correlated with ΔC/D of tacrolimus (R2=0.7). Conclusion Posaconazole significantly affects the pharmacokinetics of tacrolimus in renal transplantation patients at early stage, and individual differences are large, in which ABCB1 3435 genotype and posaconazole drug concentration are important influencing factors. The present study helps to explain the reason of individual differences in drug-drug interactions between posaconazole and tacrolimus, and provides reference for adjustment of drug dose when tacrolimus and posaconazole are used together.

Clinical usefulness of 6-TG and 6-MMP monitoring as a guide to personalize mercaptopurines treatment in patient with Autoimmune Hepatitis: a pilot study

Judit Julian[1], Dra Ana Lizana[1], Dr Ignasi Oliva[2], Dra Mª Carlota Londoño[2], Dra Mercè Brunet[3]
[1]Pharmacology and Toxicology Laboratory, Biochemistry and Molecular Genetics Department, Biomedical Diagnostic Center, Hospital Clinic of Barcelona, Barcelona, Spain, [2]Liver Unit, Hospital Clinic Barcelona, IDIBAPS, CIBEREHD, Barcelona, Spain, [3]Pharmacology and Toxicology Laboratory, Biochemistry and Molecular Genetics Department, Biomedical Diagnostic Center, Hospital Clinic of Barcelona, University of Barcelona, IDIBAPS, CIBERehd, Barcelona, Spain

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction:In recent years, clinical and scientific societies have recommended the use of algorithms that include thiopurine metabolites (6-tioguanine (6-TG) and 6-methylmercaptopurine (6-MMP)) as a guide for personalized azathioprine treatment in patients with autoimmune hepatitis (AIH). The Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group recommend the combined analysis of phenotype and genotype to adjust the treatment dose, especially in heterozygous patients with a genetic variant that affects the metabolism of these drugs. The aim of this study was to evaluate the monitoring of 6-TG and 6-MMP in erythrocytes as predictive biomarkers of individual response to azathioprine, and its potential to provide personalized therapy. Furthermore, the study examined the benefits of combining genotype and phenotype in treatment optimization.

Methods:Data from 35 patients receiving azathioprine for the treatment of AIH at Hospital Clinic Barcelona were analysed.
The genotype was analysed by qPCR and the phenotype by UPLC/MS/MS.
In 9 out of 35 patients, the genotype was determined prior to treatment initiation. Dose selection and adjustment was based on the genotype and phenotype. Clinical evolution was monitored. In 26 out of 35 patients, the genotype and phenotype were carried out at the time of patient inclusion in the study.

Results:All patients were Caucasian with a median age of 53 years, and 41% were male. Six out of 35 patients (17%) carried a of a loss-of-function variant in the TPMT gene (*1/*3A).
In 37% (14/35) of patients, the dose was changed based on the observed phenotype and genotype. Of these, 13 patients had their dose reduced, either due to the appearance of adverse effects in WT patients (n=7) or due to toxicity in those patients with a loss-of-function variant in TPMT (n=6). Only in one case was the dose increased because the patient had a functional TPMT gene and metabolites were within reference ranges.
Following the algorithm based on phenotype proposed by C. Gallardo et al., there was an 82% (29/35) correlation between the concentration of metabolites (6-TG and 6-MMP) and clinical evolution. Ten out of 35 patients had bone marrow toxicity with elevated 6-TG concentrations (>450 pmol/8•108), while 19 remained asymptomatic, and the study of metabolites confirmed that their concentrations were not elevated.
In two cases, the treatment was changed because azathioprine was not effective. In both cases, metabolite levels (6-TG and 6-MMP) were increased, indicating that azathioprine doses could not be raised further because of impending toxicity.

Conclusions:These preliminary results suggest a strong correlation between metabolite concentrations (6-TG, 6-MMP) and clinical outcomes in patients with AIH. Notably, the phenotype by

itself may identify patients with drug-related adverse events or non-responders with a wild-type genotype.
Additionally, the combination of phenotype and genotype enables early intervention for physicians to select and adjust the dose appropriately, thereby improving the efficacy and safety profile of azathioprine treatment.
In conclusion, the results from this pilot study show that the clinical implementation of this algorithm has potential to guide personalized azathioprine treatment. However, further studies in larger populations are necessary to provide more robust recommendations.

A novel LC–MS/MS Method for Therapeutic Drug Monitoring of Baricitinib in Plasma of Pediatric Patients

Dr Alessia Cafaro[1,2], Dr Giammarco Baiardi[2,3], Dr Federica Pigliasco[1], Dr Sebastiano Barco[1], Prof Francesca Mattioli[2,3], Dr Stefano Volpi[4], Dr Roberta Caorsi[4], Dr Marco Gattorno[4], Dr Giuliana Cangemi[1]

[1]Chromatography and Mass Spectrometry Section, Central Laboratory of Analysis, IRCCS Istituto Giannina Gaslini, Genoa, Italy, [2]Department of Internal Medicine, Pharmacology & Toxicology Unit, University of Genoa, Genoa, Italy, [3]Clinical Pharmacology Unit, EO Ospedali Galliera, Genoa, Italy, [4]UOC Reumatologia e Malattie Autoinfiammatorie , IRCCS Istituto Giannina Gaslini, Genoa, Italy

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction: Janus kinase inhibitors are anti-rheumatic immunosuppressive drugs that target the intracellular janus kinases (JAKs). Baricitinib is a selective and reversible orally administered JAK1/JAK2 inhibitor approved for the treatment of rheumatoid arthritis, atopic dermatitis and alopecia areata in adult patients. Safety and efficacy in children have yet to be established, and information on baricitinib pharmacokinetic properties and target plasma levels in pediatric patients is limited. We show a novel method based on liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) for the measurement of baricitinib in plasma validated according to ICH M10 guidelines.

Materials and Methods: The method is based on a protein precipitation from plasma and separation on a Thermo ScientificTM AccucoreTM Polar Premium column (50 mm × 2.1 mm, i.d. 2.6 m) after addition of deuterated internal standard. Mobile phase A consisted of 0.1% formic acid in water and mobile phase B consisting of 0.1% formic acid in ACN. The percentage of solvent B started at 2%, reached 100 % in 1 min and was kept for 1 min at flow rate of 500 µL/min, then the column was reconditioned at 2% B for 2 min for a total run time of 4 min. The column temperature was maintained at 40 ◦C. Detection was carried out using TSQ Quantiva Triple Quadrupole system (Thermo Fisher Scientific, Milan, Italy) equipped with an electrospray ionization source (ESI) operating in the positive ion mode (spray voltage at 3500 V). The specific transition of baricitinib and IS were detected using multiple reaction monitoring (MRM): 372.1→186.111 for baricitinib; 377.1→185.889, 298.815 for [2H5]-Baricitinib, respectively. The method has been successfully applied to samples from pediatric patients under baricitinib at Giannina Gaslini Institute, a tertiary care pediatric hospital.

Results: The LC-MS/MS method is linear over wide concentration ranges (1.024 – 100 ng/mL), accurate and reproducible in the absence of matrix effects allowing for a robust, specific and rapid quantification of baricitinib from a low amount of plasma (50 µL). The plasma concentration of baricitinib in the patients' anonymous samples, expressed as mean ± standard deviation, was 11.25 ± 10.86 ng/mL.

Discussions and Conclusions: The availability of analytical methods for the reliable quantification of drugs in patients’ plasma are essential to help improving TDM practice and characterize baricitinib pharmacokinetic/pharmacodynamic profile. The novel LC-MS/MS method is suitable for therapeutic drug monitoring of baricitinib and could be of help for the optimization of therapies in pediatric patients.

Exploring the exposure-response relationship of guselkumab in chronic plaque psoriasis: preliminary results

Dr. Rani Soenen[1], Dr. Lisa Schots[1], dr. Lynda Grine[1], dr. Debby Thomas[2], Prof. dr. Jo Lambert[1]
[1]Ghent University Hospital, Ghent, Belgium, [2]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium

Biologicals, Sal B, september 26, 2023, 13:00 - 14:30

Introduction: Guselkumab is the first-in-class IL-23 inhibitor approved to treat moderate-to-severe plaque psoriasis. Although the favorable benefit-risk ratio of guselkumab has been shown in four randomized controlled trials (i.e. VOYAGE 11, VOYAGE 22, NAVIGATE3, and ECLIPSE4 still not all patients respond optimally to this one-size fits all dosing approach in real-life. To this end, therapeutic drug monitoring (TDM) which allows drug optimization, based on the measurement of drug concentrations and/or anti-drug antibodies (ADA), has been suggested as a valuable tool. Therefore, the aim of this explorative trial is to explore the exposure-response relationship of guselkumab in a real-life setting.
Materials and Methods: We determined guselkumab concentrations in sera from 75 patients with psoriasis at multiple timepoints (Weeks 0, 1, 2, 3, 4, 12, 20, 28, 36, 44 and 52. After week 52, blood could be taken at an additional three timepoints. Drug levels were determined by using an in-house guselkumab immunoassay consisting of a combination of MA-GUS9F6 as capture antibody and MA-GUS12G12, conjugated to biotin, as detecting antibody. At each hospital visit, disease severity was assessed using the Psoriasis Area and Severity Index (PASI).
Results: A significant correlation was found between guselkumab serum trough concentrations and clinical response. In addition, a difference in guselkumab serum trough concentrations was found between optimal and suboptimal responders in maintenance, starting from week 4. Based on receiver operating characteristic (ROC) analysis, we concluded that the target concentration of guselkumab was 1.6 µg/ml in steady-state. No correlation between guselkumab trough concentrations and albumin was found.
Conclusions: At week 4, a distinction between optimal and suboptimal responders can be made based on guselkumab exposure, allowing timely dose modifications or treatment switch when needed. At steady-state, targeting a guselkumab serum trough concentration of 1.6 µg/ml may be a viable treatment option in suboptimal responders to prevent underexposure and subsequent suboptimal clinical response.

Determination of the optimal Ganciclovir and Valganciclovir starting dose to achieve AUC targets in children using a Machine Learning approach

Laure Ponthier[1,2], PharmD/PhD Benedicte Franck[3], MD/PhD Julie Autmizguine[4,5], PharmD/PhD Jean Baptiste Woillard[2]
[1]Pediatric intensive care unit, Limoges, France, [2]INSERM U 1248 Pharmacology and Transplantation, Limoges, France , [3]Pharmacology, Rennes, France, [4]Department of Pediatrics, Montreal , Quebec, Canada, [5]Department of Pharmacology and Physiology, Montreal, Quebec,Canada

Miscellaneous 2, Møterom 5, september 26, 2023, 13:00 - 14:30

Introduction: Cytomegalovirus (CMV) is a severe pathogen in children whose immune system is compromised or immature. The most frequently used drug for CMV disease or CMV prevention in this population are intravenous ganciclovir (GCV) or valganciclovir (VGCV). GCV and VGCV show a large interindividual pharmacokinetic variability, particularly in pediatric transplant patients. The objectives of this study were: (i) to develop a Machine learning algorithm trained on synthetic PK profiles obtained by Monte Carlo simulations based on 4 POPPK models from the literature to estimate the best GCV or VGCV starting dose to achieve target AUC; and (ii) to compare its performances on real profiles with previously published and validated equation derived from the published POPPK models.
Materials and methods: The parameters of 4 previously published POPPK models of ganciclovir in children in addition to WHO growth curve for covariates were used in the mrgsolve R package to simulate 18000 PK profiles. ML algorithms were developed from these simulations based on Xgboost, Neural networks, Random Forests and the stack of the 3 algorithms and were comparatively evaluated in the training set. The best algorithm was used to calculate the ML first dose associated with the highest probability to achieve the target. Performances were evaluated in an external set of 32 real patients for ganciclovir and in an external set of 31 patients for valganciclovir and the ML first dose was compared to the other doses recommended in the literature.
Results: The Stack of the 3 ML models yielded the best performances for GCV or VGCV. In the simulation set, the ML dose yielded the highest target attainment rate (defined by an AUC between 40 and 60 mg*h/L) (47.5% for GCV and 45.2% for the VGCV). With real patients, the ML dose for VGCV yielded the highest target attainment rate (38.2%) while for ganciclovir infusion, target attainment rate was the highest for the Franck et al model and the ML algorithm was the second best (22.6% for Franck Model vs 19.4% for ML dose).
Conclusion: The ML algorithms developed to estimate the starting dose of VGCV in children exhibit very good performances in comparison to previous validated models and should be evaluated prospectively. Nevertheless, considering the average low target attainment, TDM should be performed after the starting dose to individualize the dose and increase the target attainment.

Clinical validation of volumetric-absorptive microsampling device for mycophenolic acid determination in pediatric patients after renal transplantation

PharmD Tomasz Pawiński[1], MSc Arkadiusz Kocur[1,2], Dr Jacek Rubik[3], MSc Agnieszka Czajkowska[2]
[1]Department of Drug Chemistry, Medical University of Warsaw, Warsaw, Poland, [2]Department of Biochemistry, Radioimmunology, and Experimental Medicine, Pharmacokinetics Laboratory, The Children`s Memorial Health Institute, Warsaw, Poland, [3]Department of Nephrology, Kidney Transplantation, and Arterial Hypertension, The Children`s Memorial Health Institute, Warsaw, Poland

Immunosuppression 2, Sal D, september 26, 2023, 13:00 - 14:30

1. Introduction

Kidney transplantation (KTX) is the gold standard for renal replacement therapy in paediatric patients with end-stage renal disease (ESRD) patients. In this group, several differences between children and adults were observed, including post-transplantation complications, graft mismatch, problems related to growth, and primarily substantial non-adherence to therapy. Therefore, additional details regarding the specificity of transplantation and immunosuppressive therapy in this age group are needed. KTX must be treated as a beneficial procedure in pediatric patients because it prevents long-term dialysis and improves the quality of life. Based on the IATDMCT and EMA recommendations according to clinical validation, this process is necessary to successfully implement the validated analytical method in routine drug monitoring. The aim of this study was the full clinical development of a previously validated LC-MS/MS method based on the VAMS technique in paediatric recipients.

2. Materials and Methods

Clinical validation was performed based on the guidelines for dried-blood-spot validation using 90 samples obtained with VAMS from 30 stable renal transplant recipients treated with MMF at the Children's Memorial Health Institute in Warsaw. Differences between the methods were assessed using the Passing-Bablok regression. Two routes were considered equivalent: one within the 95% confidence interval (CI) for the slope and 0 within the 95% CI for the intercept. Based on the EMA guidelines, the differences between methods checked with the Bland-Altman plot should be less than 20% for 67% of the analysed pairs. The clinical acceptance criterion for paired sample bias was < 15% for 67% of the pairs analysed. Correlations between the methods were assessed using Pearson and within-class correlation coefficients (ICC). Following the IATDMCT guidelines for predictive performance, statistical factors, such as MPPE, MAPE, RMSE, and APE, were calculated.

3. Results

A strong relationship was observed for the paired WB and VAMS-based method samples. High Pearson’s and ICC values (>0.99) confirmed the appropriate correlation between the methods. Passing–Bablok regression confirmed high correlations for the above relationship; the intercept and slope were within the statistical acceptance criteria for comparison of VAMS and WB-based LC-MS/MS methods. The mean difference in the case of WB/VAMS was acceptable and within the EMA acceptance criteria (<20%) and the IATDMCT clinical criteria (<15%). Statistical predictive performance factors fulfilled the EMA and IATDMCT criteria (<15%).

4. Discussions and Conclusions

The present study is the first to develop an LC-MS/MS method based on WB, plasma, and VAMS to detect MPA in the pediatric population after kidney transplantation. In addition, this study might be implemented in routine clinical practice because of the satisfactory validation results and the relatively high number of patients included in the trial.

External evaluation of longitudinal population pharmacokinetic models in patients with osteoarticular infections

Dr Van Dong Nguyen[1,2], Ms Alice Côté[1], Dr Amélie Marsot[1]
[1]Faculty of Pharmacy of University Of Montreal, Montreal, Canada, [2]Department of Pharmacy of McGill University Healthcare Center, Montreal, Canada

Pharmacometrics, Møterom 5, september 25, 2023, 13:00 - 14:30

Introduction: As the risk vancomycin induced nephrotoxicity increases with duration of therapy, clearance and distribution of vancomycin become difficult to predict in the context of long term treatment which is often required for osteoarticular infections. Currently, there is a paucity of populational pharmacokinetic (popPK) models for vancomycin in the literature that addresses the longitudinal changes of pharmacokinetic parameters during an extended course of treatment. The objective of this study is to identify longitudinal popPK models for vancomycin published in the literature and assess their predictive performance for a local population with osteoarticular infections.

Material and methods: Data collection was performed in two phases; a retrospective phase with inclusion of all eligible individuals between December 1st 2020 and April 17th 2022 and a prospective phase with recruitment of eligible participants between April 18th 2022 and December 22nd 2022 who consented to provide supplementary vancomycin serum levels. A literature search was conducted in the Embase/Pubmed database using the terms referring to “vancomycin”, “population-pharmacokinetic”, “time varying”, and “osteoarticular infection” to identify longitudinal popPK models. Model performance was assessed with median predictive error (MDPE) for bias, median absolute predictive error (MDAPE) for inaccuracy and normalized distribution prediction error (NDPE). Model predicted concentrations and performance metrics were obtained using NONMEM (version 7.5, ICON 2023), R (version 4.2.2; R Core Team 2022) and Microsoft Excel (version 2016).

Results: Seventy-three individuals admitted to the orthopedic or internal medicine service at the Montreal General Hospital receiving IV vancomycin for osteoarticular infections were included in the study and provided 525 vancomycin serum concentrations for analysis of model predictive performance. The mean age and weight (SD) in the study population were 56.3 years (17.5) and 81.5 kg (23.4), respectively. Two models were retained for analysis of predictive performance. The first consisted of a one-compartment model that included covariates for neurosurgical procedure, hepatic impairment and nephrotoxic medications and was comprised of two sub-models for early phase and late phase of treatment. The second consisted of a two-compartment model that included covariates for baseline renal function and renal function at different timepoints in order to model the effect of time varying changes in renal function on pharmacokinetic parameters. Both models showed inadequate predictive performance for local population. First and second models have MDPE values of -21.0% and 76.9% and MDAPE values of 34.2% and 78.7%, respectively. Additional analysis showed significant residuals for both models in the early stage of treatment.

Discussion and conclusion: This study confirms the sparsity of longitudinal popPK models for vancomycin in the literature. In addition, these models may not be applicable for all populations. These findings suggest the need for adjustment of existing models or the development of new longitudinal models. Further efforts to address longitudinal pharmacokinetic changes for vancomycin should take into account other clinical factors such as the degree of systemic inflammation that may fluctuate significantly in the early stages of treatment and consider alternative methods to integrate the duration of treatment and longitudinal components in the model structure.

TDM of tyrosine kinase inhibitors via VAMS collection at home

Dr Nick Verougstraete[1,2], Prof Christophe Stove[2]
[1]Department of Laboratory Medicine, Ghent University Hospital, Gent, Belgium, [2]Laboratory of Toxicology, Ghent University, Gent, Belgium

Alternative Sampling Strategies 1, Møterom 1, september 25, 2023, 13:00 - 14:30

Introduction: Therapeutic drug monitoring (TDM) of tyrosine kinase inhibitors (TKIs) may improve treatment outcome and therapy individualization for oncology patients. Compared to plasma, the standard TDM matrix, dried blood microsampling is associated with several advantages, including the collection of samples by the patients themselves in their home-setting. This is especially convenient when sampling should be performed at specific time points, e.g. for the determination of trough levels of TKIs in chronic myeloid leukemia (CML) treatment, thus avoiding the risk of delayed drug intake. There is also a benefit when multiple samples should be taken in a relatively short time period, e.g. while participating in a pharmacokinetic or clinical study. The aim of this study was to evaluate the feasibility of performing TDM of TKIs, used for treatment of CML, via volumetric absorptive microsampling (VAMS) at home, and to gain insight into the inter- and intra-individual variation in TKI trough levels.

Methods: Upon inclusion, CML patients treated with bosutinib, dasatinib, imatinib, nilotinib or ponatinib were instructed on how to perform the collection of capillary VAMS samples. The participants received five sampling kits (4 sampling time points + 1 spare), each including 2 VAMS devices, an automatic lancet, a desiccant, a gauze and an instruction folder, containing images, written instructions and a link to an explanatory online video. The participants were instructed to collect the VAMS samples in duplicate just before their next TKI intake every three days, on four occasions. Consequently, for each participant eight (4x2) home-collected VAMS samples should be available. The patients were instructed to put the dried VAMS samples in a plastic bag containing desiccant. After collection of all the VAMS samples, the plastic bags were packed in a pre-paid and addressed envelope, and sent back to the lab via regular mail. In addition, the participants received a questionnaire on their perception of the VAMS collection.

Results: To date, from 50 patients home-collected VAMS samples in duplicate were received (bosutinib 1; dasatinib 24; imatinib 14; nilotinib 6 and ponatinib 5), resulting in a total of 400 samples. 355 (89%) samples were considered to be of good quality: upon receipt, samples were visually checked to verify whether they were under- (n= 34; 8.5%) or overfilled (n= 11; 2.8%). Furthermore, an acceptable analytical variability was obtained on duplicate home-collected VAMS samples (CV ranging from 7.52 to 15.6%). The obtained TKI results in these VAMS samples confirmed the large inter-patient variation in TKI trough levels and revealed that within a patient trough levels may vary substantially, especially for dasatinib. Lastly, collection of VAMS samples at home was positively received by most participants, as could be deduced from the responses to the questionnaire: most participants found the instruction folder very clear, experienced the self-collection as very convenient and judged VAMS collection in a home-setting as very user-friendly.

Conclusions: The feasibility and real-life applicability of performing TDM of TKIs, used for treatment of CML, via VAMS collection at home, was demonstrated in this study.

Quantification of rifampicin in a small volume of human plasma by UPLC-MS/MS with addressing the carryover issue

Takuya Sano[1], Takuho Ishii[1], Koichiro Hotta[2], Dr. Yuji Mano[2,3]
[1]Sunplanet Co., Ltd., Tsukuba, Japan, [2]Eisai Co., Ltd., Tsukuba, Japan, [3]University of Tsukuba, Tsukuba, Japan

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction: In the development of drugs whose clearance pathway is predominantly via cytochrome P450 (CYP) 3A, drug-drug interaction (DDI) studies as a victim of drugs by concomitant dose of CYP3A inducers are required. Rifampin (RIF) is a typical CYP3A inducer and has been frequently used in the CYP3A induction DDI assessment. Quantification of RIF is important to ensure its exposures in the systemic circulation at expected levels and thus an assay of RIF in small volume of human plasma has been developed. In assay development, a carryover has turned out to be an issue to address for accurate quantification of RIF in human plasma. In this study, we optimized ultra-performance liquid chromatography (UPLC) conditions and the established UPLC-MS/MS assay has been validated to support a clinical DDI study of drugs with RIF as a CYP3A inducer.
Materials and Methods: RIF was extracted from only 0.02 mL of human plasma by a simple protein precipitation and detected by a selected reaction monitoring in the positive ion mode. RIF and a stable isotope as an internal standard were chromatographed on a reverse phase column under gradient elution condition. Three mobile phases were used with one mobile phase having a high fraction of organic solvent with 1% formic acid was used exclusively to flush the system to minimize carryover of RIF in this assay. A method validation study was performed in accordance with the bioanalytical guidelines. In the validation study, linearity, selectivity, carryover, accuracy and precision in reproducibility, dilution integrity, extraction recovery, matrix effects, effects by hemolysis or hyperlipidemia, and comprehensive stability were assessed. Incurred sample reanalysis (ISR) was conducted to ensure reproducibility of the assay using postdose samples.
Results: Changes in the elution of the mobile phases addressed the carryover issue. RIF was quantifiable from 25 ng/mL using 0.02 mL of human plasma. Accuracy and precision in the intra- and inter-run reproducibility tests were within ±15% and 15%, respectively, which met the acceptance criteria. RIF concentrations in a clinical PK study were determined by the validated assay and the ISR test demonstrated that 100% of reassay samples showed comparable data to those in the original assay.
Discussions and Conclusions: Findings in the method validation study indicate that the developed RIF assay using 0.02 mL of human plasma is simple and reproducible. The assay was successfully applied to a clinical PK study of RIF and the ISR test also supported the reproducibility of the assay.

CLINICAL OUTCOMES AND TREATMENT OF METHICILLIN-SUSCEPTIBLE STAPHYLOCOCCUS AUREUS BACTERAEMIA (COATS STUDY)

Dr Rekha Pai Mangalore[1,2], Mr Jeff Shao[1,2], Ms Lucy Tang[1,2], Ms Qiaoran Tu[1,2], Dr Amin Hajamohideen[3], Dr Simran Bhopal[4], Prof Trisha Peel[1,2], Prof Andrew Udy[1,2], A/Prof Denis Spelman[1,2], Prof Anton Peleg[1,2]
[1]Alfred Health, Melbourne, Australia, [2]Monash University, Melbourne, Australia, [3]St Vincent's Hospital, Melbourne, Australia, [4]Royal Children's Hospital, Melbourne, Australia
Anti-infectives 1 - antibiotics and antifungals, Sal B, september 25, 2023, 13:00 - 14:30

Introduction:
Flucloxacillin has been associated with higher nephrotoxicity rates when used in the treatment methicillin-susceptible Staphylococcus aureus bacteraemia (MSSA-B). The exact mechanism remains unclear. This single-centre, retrospective study aims to examine the incidence of nephrotoxicity in penicillin and methicillin-susceptible SAB and the potential relationship between flucloxacillin doses and the occurrence of nephrotoxicity.

Methods:
We retrospectively analysed the of clinical outcomes of adult patients (aged ≥ 18y) with MSSA-B admitted to The Alfred Hospital in Melbourne from 2018 – 2021. We excluded pre-existing dialysis-dependence, mortality prior to blood culture identification, and polymicrobial bacteraemia.

Results
Results:
One-hundred sixty-six patients met inclusion criteria. Median age: 60y (IQR, 40-75); males: 120 (72%). Median Charlson comorbidity index was 3 (IQR, 1 - 4). Overall 206 co-morbid conditions were present amongst the 166 patients. Diabetes mellitus (n=31, 16%) and immune compromise (n=35, 17%) were frequently reported co-morbidities. The most common acquisition was community acquired (n=126, 75.9%) and infective endocarditis (n=30, 45.5%) was the most common diagnosis, followed by skin and soft tissue (n=21, 12.7%), spinal and psoas abscesses (n= 19, 11.5%) and osteoarticular infections (n=16, 9.6%). Initial antibiotic of choice: intravenous (IV) flucloxacillin (n=91, 55%), cefazolin (n=58, 35%). The most commonly used doses included IV flucloxacillin 2g q4h (n=55, 60%) and IV cefazolin 2g q8h (n=52, 90%). Nephrotoxicity occurred in 15 patients (flucloxacillin n=13/91, 14%; cefazolin n=2/58, 3.5%). Overall nephrotoxicity was observed in 27 patients in 19 patients (20.9%) on flucloxacillin and 8 patients (13.7%) on cefazolin. Antibiotic-attributed nephroxtoxicity was observed in 11 patients (flucloxacillin, n = 8, 9%; cefazolin, n=3, 5%). More nephrotoxicity was observed with higher dose flucloxacillin (2g q4h, n=6/55, 10.9%) than with lower doses (n=2/36, 5.6%); Odds ratio, OR, 1.96 (95% CI: 0.33, 20.8). This finding was not statistically significant (p=.07).

Discussion and conclusion:
While cases of nephrotoxicity were numerically higher in the high dose flucloxacillin group, no statistically significant association was observed. The major limitations of this study being retrospective study design and small sample size. The association between flulcoxacillin and toxicity warrants further study. Larger, prospective pharmacokinetic studies are needed to explore the dose-exposure-toxicity of flucloxacillin.

Individualized Cefepime Dosing for Febrile Neutropenia in Patients with Lymphoma or Multiple Myeloma

Dr. Kazutaka Oda[1], Ms. Ayami Yamaguchi, Mr. Naoya Matsumoto, Dr. Hirotomo Nakata, Dr. Yusuke Highchi, Dr. Kisato Nosaka, Dr. Hirofumi Jono, Dr. Hideyuki Saito
[1]Kumamoto University Hospital, Kumamoto, Japan

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

1. Introduction

Cefepime is a broad-spectrum, fourth-generation cephalosporin that effectively treats febrile neutropenia caused by gram-positive and negative organisms, including Pseudomonas aeruginosa. However, its dose-dependent neurotoxicity, such as encephalopathy, poses a challenge in determining the optimal dose. This study aimed to demonstrate the feasibility of determining individual pharmacokinetics and the appropriate dose of cefepime and evaluate the necessary exposure for optimizing clinical response.

2. Material and Methods

This prospective observational study (approval No. 2,413) enrolled patients with lymphoma or multiple myeloma who were administered cefepime for the treatment of febrile neutropenia with a single dose of 2 g every 12 h. The cefepime concentrations were monitored at 1 h (as the peak point: Cmax), 7.2 h (as 60%-time course point during the administration interval of 12 hours, C7.2h), and 11 h (immediately before the next dose, trough concentration) after the first drip infusion (rate, 2 g/1 h). The primary endpoint was the predictive performance for individual cefepime pharmacokinetics, and the secondary endpoints were the impact of cefepime pharmacokinetic parameters on clinical response and providing dosing strategies based on population pharmacokinetic analysis.

3. Results

Sixteen patients participated in the study. The mean (SD) concentrations of cefepime were 74.2 (14.2), 10.8 (8.0), and 5.0 (4.2) μg/mL at Cpeak, C7.2h, and trough, respectively. Using popPK analysis, the mean (SD) AUC was determined to be 689.7 (226.6) μg・h/mL, which correlated with C7.2h (R2=0.90) and Bayesian posterior AUC using only trough concentration (R2=0.88). Although higher exposure was associated with a better clinical response, statistical analysis did not reveal a significant difference between positive and negative clinical response for creatinine clearance (Ccr), C7.2h, trough concentration, and AUC (P = 0.0907, 0.2523, 0.4079, and 0.1142, respectively). Receiver operating characteristics analysis showed that the cut-off value for Ccr was 80.2 mL/min (sensitivity: 0.889, specificity: 0.714, area under the curve: 0.762), C7.2h was 18.6 μg/mL (sensitivity: 0.571, specificity: 1.000, area under the curve: 0.683), and trough concentration was 9.2 μg/mL (sensitivity: 0.571, specificity: 1.000, area under the curve: 0.635). The popPK model facilitated dosing strategies; continuous infusion with 4 g/day achieved 100% probability at the minimum inhibitory concentration (MIC) of 8 μg/mL, even in patients with a Ccr value of 150 mL/min. Regarding intermittent infusion, 2 g/dose every 8 h using 3-h drip infusion showed more than 80% probability at the MIC value of 4 or 8 μg/mL in patients with a Ccr value of 90 or 60 mL/min, respectively.

4. Discussions and Conclusions

While Ccr may aid in individualized dosing, C7.2h or trough concentration sampling may facilitate rapid dose optimization, especially concerning subexposure with 2 g/dose every 12 h. Taken together, this study suggests performing therapeutic drug monitoring of cefepime for patients with lymphoma or multiple myeloma receiving treatment for febrile neutropenia.

Analytical and non-analytical variation may lead to inappropriate antimicrobial dosing in neonates: an in silico study

Ms Thi Nguyen[1], Dr Ranita Kirubakaran[2,3,4], Dr Hayley Schultz[5], Ms Sherilyn Wong[5], A/Prof Stephanie Reuter[5], Dr Brendan McMullan[6,7], Srinivas Bolisetty[7], Craig Campbell[8], Andrea Horvath[8], Dr Sophie Stocker[1,2,3]

[1]School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, Camperdown, Australia, [2]School of Clinical Medicine, Faculty of Medicine and Health, University of New South Wales, Kensington, Australia, [3]Department of Clinical Pharmacology and Toxicology, St. Vincent's Hospital, Darlinghurst, Australia, [4]Seberang Jaya Hospital, , Malaysia, [5]Clinical & Health Sciences, University of South Australia, Adelaide, Australia, [6]Department of Immunology and Infectious Diseases, Sydney Children's Hospital, Randwick, Australia, [7]Faculty of Medicine and Health, University of New South Wales, Kensington, Australia, [8]NSW Health Pathology, Department of Chemical Pathology, Prince of Wales Hospital, Sydney, Australia

Anti-infectives 2 - antibiotics and antifungals, Møterom 4, september 26, 2023, 13:00 - 14:30

Introduction: Therapeutic drug monitoring (TDM) of aminoglycosides and vancomycin is used to prevent oto- and nephrotoxicity in neonates. Analytical and non-analytical factors potentially influence dosing recommendations. This study aimed to determine the impact of analytical variation (imprecision and bias) and non-analytical factors (accuracy of drug administration time, use of non-trough concentrations, biological variation and dosing errors) on neonatal antimicrobial dosing recommendations.

Materials and Methods: Published population pharmacokinetic models and the Australasian Neonatal Medicines Formulary were used to simulate antimicrobial concentration-time profiles in a virtual neonate population. Laboratory quality assurance data were used to quantify analytical variation in antimicrobial measurement methods used in clinical practice. Guideline-informed dosing recommendations based on drug concentrations were applied to compare the impact of analytical variation and non-analytical factors on antimicrobial dosing.

Results: Analytical variation caused differences in subsequent guideline-informed dosing recommendations in 9.3−12.1% (amikacin), 16.2−19.0% (tobramycin), 12.2−45.8% (gentamicin), and 9.6−19.5% (vancomycin) of neonates. For vancomycin, inaccuracies in drug administration time (45.6%), use of non-trough concentrations (44.7%), within-subject biological variation (38.2%) and dosing errors (27.5%) were predicted to result in more dosing discrepancies than analytical variation (12.5%). Using current analytical performance specifications, tolerated dosing discrepancies would be up to 14.8% (aminoglycosides) and 23.7% (vancomycin).

Discussion and Conclusions: Although analytical variation can influence neonatal antimicrobial dosing recommendations, non-analytical factors are more influential. These result in substantial variation in subsequent dosing of antimicrobials, risking inadvertent under- or over- exposure. Harmonisation of measurement methods and improved patient management systems may reduce the impact of analytical and non-analytical factors on neonatal antimicrobial dosing.

Quantification of vancomycin and creatinine in dried blood spot using liquid chromatography – tandem mass spectrometry: method development, validation, and clinical application

Bsc Soma Bahmany[1], MSc Moska Hassanzai[1], Dr Robert Flint[1], Dr Hein van Onzenoort[2], Dr Brenda C.M. de Winter[1], Prof. Dr. Birgit C.P. Koch[1]
[1]Erasmus Medical Center, Rotterdam, Netherlands, [2]Radboud Medical Center, Nijmegen, Netherlands
Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Vancomycin is a widely used antibiotic for the treatment of gram-positive bacterial infections, especially in case of methicillin-resistant Staphylococcus aureus (MRSA) infections. Due to several toxic side effects, such as the 'red man syndrome', nephrotoxicity, and ototoxicity, vancomycin has a narrow therapeutic window. Therefore, therapeutic drug monitoring (TDM) is recommended to minimalize toxicity and maximize treatment efficacy. Venous blood sampling is mostly applied in clinical settings for the quantification of vancomycin, although this widely used sampling method is more painful and invasive compared to more patient friendly alternatives, such as the dried blood spot (DBS) method. For the quantification of vancomycin immuno-assays are widely used, due to quick measurement. However, cross-reactivity with metabolites and degradation products should be taken into account when using this technique. Vancomycin clearance is highly correlated with creatinine clearance. Hence, we successfully developed and validated a quantification method for the simultaneous determination of creatinine and vancomycin in DBS in one single run making use of liquid chromatography coupled by tandem mass spectrometry (LC-MS/MS). Sample preparation was performed by punching out a 6 mm spot of the DBS cards into a cryo tube. 400 µL of the internal standard solution (2.5 mg/L of vancomycin-d12, 5 µmol/L creatinine-d3 and 1% formic acid in methanol:MilliQ 50: 50% v/v) was added to all samples and vortexed for 10 seconds. After vortexing, samples were sonicated in a water bath for 20 minutes at 40°C. Subsequently, 200 µL of each extract was pipetted into an autosampler insert vial and 2 µL of each extract was injected into the UPLC system. Chromatographic separation was performed by using a Waters Acquity UPLC HSS T3 C18 column (1.8 µm, 2.1 x 100 mm). Mobile phase B (MP) consisted of 2 mM ammonium acetate and 0.1% formic acid in 1L of methanol. Column temperature was set at 45°C, flow rate was set at 0.35 mL/min. and total run time was 5.2 minutes. The electrospray ionization was performed in positive mode. Validation of this analytical method was performed based on the EMA guidelines and FDA guidelines. Validation included the following parameters: linearity, limits of quantification, accuracy, inter-day and intra-day precision, carry-over, autosampler stability, short-term and long-term stability, the influence of different spot volumes on the DBS cards, the drying time and storage condition of the spots, recovery and the hematocrit (Ht) effect. The method was found linear ($r^2 > 0.990$) for both compounds. The inaccuracies and imprecisions were <15% for both compounds. Matrix effects and recoveries were within 15% consistent with coefficient of variations of less than 15%. No significant carryover effect was observed. We successfully developed and validated a fast and accurate quantification method for the simultaneous determination of vancomycin and creatinine making use of a patient friendly sampling method. The fast and efficient sample preparation and short analysis run time make this method highly suitable for hospital settings and for patients at home using vancomycin.

Stakeholder perspectives on the barriers and enablers of beta-lactam antibiotic therapeutic drug monitoring: a qualitative analysis

Dr Rekha Pai Mangalore[1], Prof Trisha Peel[1], Prof Andrew Udy[1], Prof Anton Peleg[1], Dr Darshini Ayton[2]
[1]Alfred Health/Monash University, Melbourne, Australia, [2]Monash University, Melbourne, Australia
Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction
Beta-lactam antibiotic (beta-lactams) therapeutic drug monitoring (TDM) is increasingly recommended for optimising antibiotic exposure in septic intensive care patients. Limited data are available on the implementation of beta-lactam TDM within complex healthcare settings. We used theory-based approaches to systematically explore the barriers and enablers perceived by key stakeholders to the implementation of beta-lactam TDM in the intensive care unit (ICU).

Methods
A qualitative descriptive study was conducted as a part of a broader TDM implementation project. This single-centre study was conducted at a large metropolitan tertiary referral centre. The centre has a large ICU with approximately 55 beds and provides several state-wide services (trauma, burns, extra-corporeal membrane oxygenation, transplant). Key stakeholders were purposively sampled and interviewed, including infectious disease physicians, ICU physicians, pharmacists, clinical leaders, scientists and nurses. Data were thematically analysed and coded using the theoretical domains framework (TDF) and mapped to the relevant domains of the COM-B (capability, opportunity, motivation) behaviour change model.

Results
A total of 40 interviews (18 physicians, 17 pharmacists, three nurses and two laboratory participants) were conducted. The following main barriers emerged: (a) Lack scientific knowledge, evidence and experience (b) Lack of access to resources education (c) Fear of causing harm to patients. The main enablers included (a) Access to education, experts and resources (b) Access to onsite assays with short turnaround times (c) Clear channels of communication within and amongst teams and (d) Endorsement by hospital leadership. Improving patient care and outcomes, trust in colleagues, and, endorsement by hospital leadership were strong motivators. Pharmacists and nursing stakeholder groups emerged as key targets of implementation strategies.

Discussion and conclusions
The key implementation strategies included: targeted and tailored (stakeholder specific) education; development of easy to access standardised guidelines and protocols; establishment of governance with clear channels to escalate complex cases and endorsement by senior leadership; integration of workflows - integration of TDM discussions and processes within existing workflows, integration of TDM processes into electronic health record systems (online ordering, availability of results) and regular audit, feedback and research.
Using theory-based approaches we have identified the key barriers and enablers to the establishment of beta-lactam TDM. We have used these data to identify key strategies, policies, and target groups for implementation interventions.

Fully Automated LC-MS/MS Analysis of Aminoglycoside and Glycopeptide antibiotics

Kohei Yoshikawa[1], Toshikazu Minohata[1]
[1]Shimadzu Corporation, Kyoto, Japan

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

1.Introduction

Aminoglycosides and glycopeptide antibiotics are widely used in clinical treatment of serious infections with a good clinical effectiveness, a low rate of true resistance and low cost. Aminoglycosides have a narrow therapeutic range, and high plasma concentrations may lead to toxicity. To achieve maximum efficacy while minimizing side effects for bacterial infections, it is necessary to control the plasma concentration.
HPLC is commonly used for drug analysis in biological samples. While analysis methods using optical detectors have been widely reported, mass spectrometry-based methods are becoming mainstream because of their selectivity and the ability to analyze multiple drugs simultaneously in a short time. In this study, we evaluated a method for analyzing aminoglycosides in plasma based on triple quadrupole mass spectrometry. In addition, we evaluated pretreatment process using a fully automatic pretreatment device.

2.Materials and Methods

We prepared a mixed sample of the aminoglycoside (amikacin, tobramycin, gentamycin etc.) and glycopeptide (vancomycin) antibiotics and added it to plasma for use in evaluating the analysis method. The calibration curve range was set to include the therapeutic range. We used an ultra-high performance liquid chromatograph Nexera™ X3 and a triple quadrupole mass spectrometer LCMS-8060. Separation was performed on a Shim-pack GIST-HP Amide (Metal-free, 3 µm, 50 mm×2.1 mm). Sample preparation was carried out by a fully automatic pretreatment device CLAM™-2040. CLAM-2040 can add internal standard solution and organic solvent for protein precipitation, and filtrated solution was automatically transported to autosampler for LC-MS/MS analysis. The LC-MS/MS analysis took about 3 min.

3.Results

We analyzed nine calibration curve samples in the range of 0.5-50 mg/L. Calibration curves were obtained with R^2 values of 0.99 or higher for each compound by internal standardization using a linear or quadratic regression model. In addition, accuracy was within 100±15% for each point for each compound, and precision (% RSD) was within 15%.

4.Discussions and Conclusions

We evaluated the analytical method for aminoglycoside and glycopeptide antibiotics using a triple quadrupole mass spectrometer with a fully automated sample preparation device. We obtained good calibration curves for all components and were able to measure each sample in 4 minutes. The automated sample preparation process enables simple and safe analysis.

A model-based pharmacokinetic analysis of drug-drug interaction between nirmatrelvir/ritonavir and tacrolimus

Dr. Kotaro Itohara[1], Mr. Takeshi Tomida[1], Dr. Kazuhiro Yamamoto[1], Dr. Takeshi Kimura[1], Mr. Kohei Fujita[1], Dr. Atsushi Uda[1], Dr. Yumi Kitahiro[1], Dr. Naoki Yokoyama[2], Dr. Yoji Hyodo[2], Dr. Tomohiro Omura[1], Dr. Ikuko Yano[1]
[1]Department of Pharmacy, Kobe University Hospital, Kobe, Japan, [2]Division of Urology, Kobe University Graduate School of Medicine, Kobe, Japan

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

[Introduction]
Nirmatrelvir/ritonavir (Paxlovid) is used for treating mild to moderate COVID-19 at high risk of progression to severe disease. Ritonavir is a strong inhibitor of cytochrome P450 (CYP) 3A and P-glycoprotein, and is known to cause drug-drug interactions with various drugs including tacrolimus. Some cases with tacrolimus withdrawal during nirmatrelvir/ritonavir administration have been reported, but pharmacokinetic assessment during the concomitant use of both drugs was limited. We experienced a patient with remarkable and prolonged increase in blood tacrolimus concentrations when nirmatrelvir/ritonavir was concomitantly used. In this study, the effects of nirmatrelvir/ritonavir on tacrolimus pharmacokinetics were examined using a model-based pharmacokinetic analysis.
[Patients and Methods]
A renal transplant patient taking oral tacrolimus continuously was treated with nirmatrelvir/ritonavir for 5 days. The baseline tacrolimus dose and trough blood concentration were 2.5 mg/day and 4.2 ng/mL, respectively. Although tacrolimus was discontinued at 6 days after the start of nirmatrelvir/ritonavir, the blood tacrolimus concentration markedly increased to 96.4 ng/mL at 7 days after the start of nirmatrelvir/ritonavir treatment. Six more days were needed for blood tacrolimus concentration to decrease to the same level as before the initiation of nirmatrelvir/ritonavir.
A one-compartment model with first order absorption was used to determine the pharmacokinetic parameters of tacrolimus. Pharmacokinetic parameters of tacrolimus without nirmatrelvir/ritonavir were estimated by the Bayesian method using the baseline observed concentration data and population pharmacokinetic parameters previously reported. The intensity and duration of nirmatrelvir/ritonavir inhibition to tacrolimus metabolism were estimated by model fitting to the observed blood tacrolimus concentrations.
[Results]
The apparent clearance, apparent volume of distribution, and absorption rate constant of tacrolimus without nirmatrelvir/ritonavir were estimated as 15.6 L/h, 295 L, and 0.32 /h, respectively, by the Bayesian estimation. The model analysis showed that the clearance and relative bioavailability of tacrolimus increased by 0.19-fold and 5.65-fold, respectively, during the nirmatrelvir/ritonavir concomitant use. In addition, the simulated blood tacrolimus concentrations could be best fitted to the observed concentrations when the inhibitory effect of nirmatrelvir/ritonavir was modeled to continue until 3 days after the end of the combination and then to disappear linearly over a week.
[Discussion and Conclusions]
The quantitative pharmacokinetic changes of tacrolimus during and after nirmatrelvir/ritonavir treatment were well analyzed by our constructed pharmacokinetic model. This model analysis revealed that the simulated values could be fitted to the observed values by greatly increased tacrolimus bioavailability in addition to decreased clearance when nirmatrelvir/ritonavir was concomitantly used. Additionally, since the CYP3A inhibitory mode of ritonavir is known to be irreversible, the inhibitory effects continued for approximately one week after the end of concomitant use of nirmatrelvir/ritonavir.

In conclusion, nirmatrelvir/ritonavir greatly increases blood tacrolimus concentrations by inhibiting intestinal first-pass metabolism as well as hepatic metabolism, and this drug-drug interaction should be considered about one week after stopping the concomitant use.

Automated 24/7 screening and quantification of DOACs in plasma in a single run on CLAM2030 – LCMS8050

MD Anna Abratis[1], MD, PhD Moritz Schnelle[1], PhD Frank Streit[1], MD Manuel Wallbach[2], MD Nils Kunze-Szikszay[3], MD Sebastian Uwe Schnitzler[3], MD Julie Schanz[1], MD, PhD Andreas Fischer[1], MD, PhD Ivana Markovic[1]

[1]Institute for Clinical Chemistry / Interdisciplinary UMG Laboratories, University Medical Center Goettingen, Göttingen, Germany, [2]Department of Nephrology and Rheumatology, University Medical Center Goettingen, Göttingen, Germany, [3]Department of Anesthesiology, University Medical Center Goettingen, Göttingen, Deutschland

Miscellaneous 2, Møterom 5, september 26, 2023, 13:00 - 14:30

1. Introduction

In recent years, therapeutic drug monitoring (TDM) as part of DOAC therapy has gained in importance, since the outcome can be improved through individual dose adjustment, especially when treating critically ill emergency patients. At present, the effects of various DOACs are usually assessed indirectly and insufficiently (e.g. by determining the thromboplastin time or the activated partial thromboplastin time). Liquid chromatography with tandem mass spectrometry (LC-MS/MS) is an appropriate system for simultaneous measurement of multiple drugs. Until today, however, the use of LC-MS/MS Systems in emergency labs were not yet established.

Therefore, this study aims to develop and to validate a new LCMS-based method to screen and quantify different DOACs simultaneously in a single run. Similar methods have so far been restricted to research purposes, usually presupposing trained staff and long running times. Connecting the LCMS to an automated sample preparation module, we assessed its suitability for DOAC screening on a routine 24/7 basis. We compared the method for three of the available DOACs using the LCMS-8050 system coupled to CLAM-2030 (both Shimadzu) versus commercially available chromogenic tests.

2. Materials and Methods

The plasma samples from 56 anesthesiologically and nephrologically supervised patients were collected. DOAC plasma concentrations of Apixaban, Dabigatran and Rivaroxaban were measured on a LCMS system through an automated sample preparation module. Sample protein precipitation and chromatographic separation with a sharp linear gradient on a fused core column at 50°C were performed automatically by CLAM-2030. The target compounds were identified by parent ions and optimized MRM transitions. Quantification was performed by using calibration curve deuterated internal standards. Quality controls were checked twice a day. In parallel, the quantitative determination of DOACs were assessed using conventional automated chromogenic tests (DTI-Assay (Dabigadran), Anti-Xa-Assay (Apixaban, Rivaroxaban), HemosIL (Werfen Company) on a IL Coagulation System (ACL TOP 750). Patient plasma samples were placed on the devices according to their arrival in the lab.

3. Results

The Screening results have shown a good correspondence with the patients' data. Passing–Bablok regression analysis revealed good comparability between the methods (Apixaban r=0.984, y=1.019*x–1.354; Rivaroxaban r=0.986, y=1.063*x–1.663; Dabigadran r=0.988, y=0.856*x–0.362). The precision of calibrations (range about 10 to 500ng/ml) and controls was within the manufacturer limit. The automated system was straightforward and proved easy to handle after short training periods. Running time including sample preparation was approx. six minutes.

4. Conclusion

The presented method is convincing in its easy handling and is conceivable for (24/7) routine measurements. In contrast to previously used methods, particularly the contemporaneous assignment and quantification of different DOACs is innovative.

Therapeutic drug monitoring of oral targeted therapies in oncology – non-successful cohorts of a multicenter prospective study

MD Maud B.A. van der Kleij[1,2], BSc Niels A.D. Guchelaar[2], PharmD Marinda Meertens[3], MD Kim Westerdijk[4], PharmD Eline L. Giraud[5], MD Roos F. Bleckman[6], PharmD, PhD Stijn L.W. Koolen[2,7], MD, PhD Ingrid M.E. Desar[4], PharmD, PhD Dirk Jan A.R. Moes[8], MD, PhD Alex L.T. Imholz[9], MD Annelie Vulink[10], MD, PhD Hans-Martin Otten[11], MD, PhD Tineke Smilde[12], MD, PhD Maartje Los[13], MD, PhD Helle-Brit Fiebrich-Westra[14], MD, PhD A. Paul Hamberg[15], PharmD, PhD Floor J.E. Lubberman[16], MD Helgi H. Helgason[17], Prof. Daan J. Touw[18], Prof. Hans Gelderblom[19], Prof. An K.L. Reyners[6], Prof. Nielka P. van Erp[5], Prof. Ron H.J. Mathijssen[2], Prof. Alwin D.R. Huitema[3,20,21], MD, PhD Neeltje Steeghs[1], On behalf of the Dutch Pharmacology Oncology Group (DPOG)
[1]Department of Clinical Pharmacology, Division of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands, [2]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands, [3]Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands, [4]Department of Medical Oncology, Radboud University Medical Center, Nijmegen, The Netherlands, [5]Department of Pharmacology, Radboud University Medical Center, Nijmegen, The Netherlands, [6]Department of Medical Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [7]Department of Pharmacy, Erasmus Medical Center, Rotterdam, The Netherlands, [8]Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, The Netherlands, [9]Department of Medical Oncology, Deventer Hospital, Deventer, The Netherlands, [10]Department of Medical Oncology, Reinier de Graaf Hospital, Delft, The Netherlands, [11]Department of Medical Oncology, Meander Medical Center, Amersfoort, The Netherlands, [12]Department of Medical Oncology, Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands, [13]Department of Medical Oncology, St. Antonius Hospital, Nieuwegein, Nieuwegein, The Netherlands, [14]Department of Medical Oncology, Isala Clinics, Zwolle, The Netherlands, [15]Department of Medical Oncology, Franciscus Gasthuis & Vlietland, Schiedam, The Netherlands, [16]Department of Pharmacy, Gelderse Vallei Hospital, Ede, The Netherlands, [17]Department of Medical Oncology, Haaglanden Medical Center, The Hague, The Netherlands, [18]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [19]Department of Medical Oncology, Leiden University Medical Center, Leiden, The Netherlands, [20]Department of Clinical Pharmacy, Utrecht University Medical Center, Utrecht, The Netherlands, [21]Department of Pharmacology, Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

Oncology, Møterom 2, september 25, 2023, 13:00 - 14:30

Introduction

Therapeutic drug monitoring (TDM) of oral targeted therapies in oncology could be a solution for the large interpatient variability in exposure of these drugs causing overdosing and underdosing(Yu et al., 2014). This variability and several other factors make these drugs suitable candidates for TDM and pharmacokinetic (PK)-guided dosing, including narrow therapeutic range, positive exposure-response relationships and the possibility to adjust the dose or dosing strategy(Groenland et al., 2019&2021). Although a recent multicenter prospective study demonstrated the feasibility of TDM and PK-guided dosing for multiple oral targeted therapies in oncology, standard TDM was not successful for some drug cohorts (https://trialsearch.who.int/;NTR6866)(Groenland et al., 2022). The aim of this abstract is to discuss why these cohorts of this ongoing trial were closed and to give insight in other factors that may play a role in the feasibility of TDM.

Methods

The feasibility of TDM and PK-guided dosing of a drug cohort was evaluated within the Dutch Pharmacology Oncology Group (DPOG) when approximately 30 patients were included within the cohort. If feasibility of PK-guided dosing was considered promising, the cohort remained open for inclusion with the aim to confirm feasibility in a larger cohort (n = 100) and to evaluate preliminary

efficacy results. If feasibility of TDM was not considered promising, the cohort was closed. Feasibility of PK-guided dosing was evaluated based on the success and possibility of PK-guided dose adjustments considering toxicity, appropriateness of targets, logistics and other unforeseen obstacles.

Results

As per 1 April 2023, feasibility of PK-guided dosing has been evaluated for 17 drug cohorts. Feasibility of TDM was considered promising for 5 drugs, for which the study remains open for inclusion. Cohorts of 12 drugs including 348 patients were closed after evaluation. Toxicity was the most common reason for the non-feasibility of PK-guided dosing, namely for cabozantinib, dabrafenib/trametinib, everolimus, sorafenib, vismodegib and regorafenib (range n = 13-68). The cohorts of enzalutamide, erlotinib and gefitinib (range n = 0-43) were closed because nearly all patients had trough concentration above the predefined target and therefore PK-guided dose adjustments were not of added value. The olaparib and palbociclib cohorts were closed for logistical reasons. The olaparib cohort (n = 36) was closed because the target was based on the average mean Cmin of the no longer used capsule formulation. The palbociclib cohort (n = 37) was closed, because the protocol was often not followed. It was impractical for patients to visit the hospital more often than usual because of the need for both evaluation of toxicity and trough level measurements. The tamoxifen cohort (n = 25) was closed because the feasibility of TDM was demonstrated in a larger cohort, and our cohort would not meet the power of that study(Fox et al., 2016).

Discussion and Conclusions

Although certain drugs might seem suitable candidates for TDM on forehand, the course of this prospective study showed that there are several factors to consider when determining the feasibility of TDM. Tolerability, non-critical targets and logistical reasons can limit the applicability of TDM in clinical practice.

TDM supported change of antibiotic administration in critícal ill patients Fully Automaten Routine TDM analysis by LC-MS/MS

Dr. rer. nat. Frank Streit[1], Gry Helene Dihazi[1], Ivana Marković[1], Thorsten Perl[2], Andreas Fischer[1]
[1]Institute For Clinical Chemistry / Interdisciplinary Umg Laboratories University Medical Center Göttingen Germany, Goettingen , Germany, [2]Department of General-, Visceral- and Pediatric surgery, University Medical Center Goettingen, Goettingen, Germany

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

1. Introduction

Therapeutic drug monitoring (TDM) plays an important role in the patient care of a maximum care provider. The ability to determine the current drug concentration in the blood, including a timely sample processing and traceability of the results, allows a rapid adjustment of the drug dosage in order to achieve optimal drug concentrations or to prevent toxicity. Mass spectrometry, a common device for the measurement of drug concentration, does usually not allow use in 24/7 routine analysis due to the complexity of the method. In recent years, we have developed 7 multiparametric LDT–procedures with the CLAM2030-LCMS8060NX (Shimadzu Corporation) and allowed a TDM supported changes of antibiotic administration in critical ill patients tocontinuous infusion therapy. However, the automation of biological sample extraction, directly coupled to LCMS, has proven to be a challenge. A fully automated platform enables methods to alternate smoothly without the need of human intervention, facilitating 24/7 use in clinical laboratories.

2. Materials and Methods

The evaluated analytical system was a fully automated platform (Shimadzu Corporation), composed of CLAM-2030 automation module, coupled to Nexera(TM)X2 UHPLC and LCMS-8060NX(TM) LC/MS/MS. HL-7 interface standards were used for bidirectional communication between the laboratory information system (LIS) (Dedalus, Germany) and the CLAM-LC/MS/MS. A separate LCMS method was developed, optimized and validated for each of the targeted applications (antibiotics, direct oral anticoagulants, antiepileptics, neuroleptics, antidepressant drugs (SSRI), tricyclic antidepressants, and benzodiazepines). All methods use similar analytical conditions, so there is no need to equilibrate the system between two different methods. In order to subject the system to the endurance test for 24/7 analysis, the various methods were requested in a randomized manner.

3. Results

Results of repeatedly randomized measured quality controls and patient samples were evaluated with respect to the area, area ratio, ion ratio, and retention time. All results were within the acceptance criteria. Individual specific acceptance criteria for analytes, as well as for stable isotopic labelled internal standards were used to verify analytical processes in terms of system check (min. response of internal standards), identification (quantifier/qualifier ratio dev.%), calculation and result transmission. These methods can also be used for screening. Identified analytes are automatically sent as a pdf-report to the LIS.

4. Conclusion

Randomized measurement of different LDT procedures and long-term stability of calibration curves are making CLAM2030-LCMS8060NX an attractive device for 24/7 use in clinical and toxicological diagnostics. Automated randomized measurements of patient samples with the LCMS8060NX system coupled to CLAM2030 requesting different LDT procedures were successfully transferred to LIS using HL-7 Interface standards, enabling its applications in 24/7 routine.

Development of covariate-informed model pooling method to predict the correct starting dose

Bram Agema[1,2], Dr. Stijn Koolen[1,2], Prof. dr. Ron Mathijssen[1], Dr. Brenda De Winter[2,3], Prof. dr. Birgit Koch[2,3], Dr. Sebastiaan Sassen[2,3]
[1]Erasmus MC Dept. of Hospital Pharmacy, Rotterdam, Netherlands, [2]Erasmus MC Dept. of Medical Oncology, Rotterdam, Netherlands, [3]Erasmus MC Rotterdam Clinical Pharmacometrics Group, Rotterdam, Netherlands

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Objectives
An increasing number of population pharmacokinetic (POP-PK) models have been developed which can predict plasma concentrations based solely on patient characteristics. However, the a priori predictive value of these models is mostly low due to a large margin of error and a high degree of inter-individual variability. In addition, it is difficult to determine which models perform best in the intended target population. To counter this problem, we developed an algorithm that pools different POP-PK models tailored to patient characteristics which we call covariate-informed model pooling (CIMP). Our aim is to decrease the proportion of patients with plasma levels outside the therapeutic window by giving a predicted starting dose. We used imatinib as a case study for this analysis.

Methods
A retrospective study was performed in 62 patients who were treated with imatinib for gastro-intestinal stromal tumors (GIST) at the Erasmus Medical Center. Steady-state imatinib plasma concentrations, laboratory values and patient characteristics were collected.
Twelve models were used to generate model-predicted imatinib concentrations for each patient. In our research we tested three different approaches to predict starting dosages. Firstly, the prediction of the model which was suited best after external evaluation of our data. Lastly the CIMP approach was implemented. In this approach the models were scored based on bias and RSME and were given more influence on the dose predictions in the specific populations in which they performed better

After obtaining the predictions, the predicted plasma concentrations were extrapolated towards a steady state trough time using the half-life, as is current practice in our hospital. Using these predicted extrapolated trough concentrations, a dose recommendation was obtained with steady-state trough levels between1100 – 2200 ng/mL as target. As no upper target limit is known for GIST patients in literature, we doubled the threshold and used this as an upper limit. When a patient was predicted to be under- or overexposed, the algorithm would augment or decrease the dose in steps of 100 mg to increase exposure. Using the extrapolated observed concentrations the result of the dosing advices were simulated

Results
Using the CIMP dose recommendations, the amount of patients outside the therapeutic window of 1100 - 2200 ng/mL was reduced by 36.4% (from 53.2% to 33.9%). When only using the best model the amount of patients outside the therapeutic window was 48.4% and when using the equal importance score for each model, this was reduced to 43.5%.
The CIMP prediction resulted in a relative bias of -4.9% and a relative RMSE of 38.8%. This was better compared to pooling all models equally (bias: -3.1%, RMSE: 45.2%) or using the best model after an external evaluation (bias: 10.1%, RMSE: 54.5%).

Conclusion
We showed that CIMP is a feasible approach for predicting drug plasma concentrations before sampling, using all available PK models including a weighting factor, which outperforms more

conventional methods. When these predictions are used to perform dose recommendations, the amount of patients below the threshold decreased by 34.6%.

Saliva-based assay to measure the concentration of pyrazinamide using a mobile UV Spectrophotometer

Mr Ricky Hao Chen[1,2], Ms Thi Nguyen[1,2], Dr Hannah Yejin Kim[1,3,4], Dr Sophie L. Stocker[1,5,6], Johannes Alffenaar[1,2,3]

[1]Sydney Pharmacy School, Faculty of Medicine and Health, The University of Sydney, Camperdown, Australia, [2]Westmead Hospital, Westmead, Australia, [3]Sydney Institute for Infectious Diseases, University of Sydney, Sydney, Australia, [4]Department of Pharmacy, Westmead Hospital, Westmead, Australia, [5]Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Darlinghurst, Australia, [6]St Vincent's Clinical Campus, School of Clinical Medicine, The University of New South Wales, Darlinghurst, Australia

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction: Tuberculosis is a leading infectious disease worldwide with higher prevalence rates in less-resourced settings. Pyrazinamide is an effective first-line drug for susceptible tuberculosis treatment. Treatment response is variable even when using a weigh-based dosing regimen due to factors such as gender, age, and body mass index. Simple and accessible strategies to optimise pyrazinamide dosing, even in less-resourced settings are therefore warranted to facilitate adequate treatment response. This study aimed to develop and validate an assay to quantify pyrazinamide concentration in saliva using a mobile UV spectrophotometer.

Materials and Methods: All reference materials were obtained from reliable manufacturers with ≥ 98% in purity. All measurements were conducted using the nano-volume drop function on the Implen NP80 mobile UV nanophotometer. Assay development involved applying second derivative spectroscopy with the Savitzky-Golay filter between wavelengths of 200 to 300 nm to measure saliva samples of spiked drug concentrations. Assay validation as per EMA and FDA guidelines included assessing selectivity, specificity, linearity, accuracy, precision, carry-over and matrix effects. Specificity was also analysed by evaluating the impact of co-administered medications on pyrazinamide results. The effect of filtration on reducing interferences of saliva samples was assessed using 0.22µm Millex-GP and GV filters. Sample stability was measured after seven days in cold (2 – 8°C), room temperature (20°C) and warm (40°C) storage conditions whereas, freeze-thaw stability was evaluated after three cycles.

Results: The calibration curve from nine data points (7.5, 10, 15, 25, 50, 75, 100, 150, 200 mg/L) was linear (R^2 = 0.9991). The overall accuracy and precision ranged from – 0.66% to 5.15%, and 0.56% to 4.95% respectively. Within-day precision was 0.91% whereas between-day precision was 7.01% at a LLOQ of 7.5 mg/L. Carry-over and matrix effects were both acceptable with an accuracy of < ± 4% and precision of < 7.5%. All co-administered medications displayed negligible interferences except levofloxacin which resulted in an accuracy bias of – 36% at an expected therapeutic concentration of 15 mg/L. This analytical interference of levofloxacin was limited to pyrazinamide concentrations < 25 mg/L and hence did not have an impact on the assay's clinical applicability. Both Millex-GP and GV filters had similar results with an acceptable < 5% in precision and a range of – 10.45% to 5.35% in accuracy for all quality control (QC) concentrations. Pyrazinamide was considered stable in saliva after seven days in all storage conditions with an acceptable precision < 6.5% and accuracy < ± 11% for both low and high QCs. Freeze-thaw stability after three cycles resulted in a precision < 1% and an accuracy < 11% for both low and high QCs.

Discussions and Conclusions: A novel point-of-care saliva-based assay for pyrazinamide has been successfully developed and validated using the mobile UV spectrophotometer to facilitate the personalised dosing of pyrazinamide in less-resourced settings. We recommend using the assay in combination with a limited sampling strategy at two and six hours, to estimate the overall drug exposure and aid clinicians in making informed dosing decisions to improve treatment outcomes.

A quantitative method for the analysis of ivacaftor, hydroxymethyl ivacaftor, ivacaftor carboxylate, tezacaftor, M1-tezacaftor, elexacaftor and M23-elexacaftor in plasma and dried blood spots using LC-MS/MS

Mrs Marloes Vos- Van Der Meer[1], PharmD Steffie E.M. Vonk[1], Dennis T.D. van der Laan[1], PharmD, PhD Yuma A. Bijleveld[1], Renate Kos[2], PhD Anke H. Maitland[2], PhD Marleen E. Kemper[1], PharmD, PhD Ron A.A. Mathôt[1]

[1]Amsterdam UMC location University of Amsterdam, Department of Pharmacy & Clinical Pharmacology, Amsterdam, The Netherlands, [2]Amsterdam UMC location University of Amsterdam, Department of Pulmonary Medicine, Amsterdam, The Netherlands

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Background:
The cystic fibrosis transmembrane conductance regulator (CFTR) modulators ivacaftor (IVA), tezacaftor (TEZ) and elexacaftor (ELX) are drugs directly targeting the underlying pathophysiological mechanism in cystic fibrosis (CF). The aim of this study was to validate a quantification method for IVA and its main metabolites hydroxymethyl IVA (M1-IVA) and IVA carboxylate (M6-IVA), TEZ and its metabolite M1-TEZ (M1-TEZ) and ELX and its metabolite M23-ELX in plasma and dried blood spots (DBS) using liquid chromatography with tandem mass spectrometry (LC-MS/MS). The analysis of CFTR modulators in DBS nor the analysis of metabolites of CFTR modulators in plasma have been published previously.

Methods:
A simple pretreatment method was used by adding protein precipitation solution (ACN:MeOH 84:16 v:v) with internal standard, containing 13C6-IVA, TEZ-D4 and ELX-D3, to each plasma sample (20 µL). The DBS (8 mm spot, Whatman 903 paper) was extracted with internal standard solution and water by vortexing and ultrasonic shaking (5 + 10 min). LC-MS/MS using a SCIEX 5500 Qtrap was performed with a total run time of 6 minutes. The method was validated by assessing linearity, accuracy and precision, dilution, selectivity, carry-over, matrix effects, stability, in plasma. For the DBS linearity, accuracy and precision, selectivity, stability, different levels of hematocrit, spot to spot carry-over and extraction efficiency were examined.

Results:
The selectivity was good as no interference from matrices was observed. In the concentration range from 0.01 to 10.0 mg/L (M1-TEZ 0.05 to 25 mg/L), calibration curves were quadratic with a correlation coefficient >0.9997 for all compounds in both plasma and DBS.
In plasma samples, within-run and between-run accuracy were between 95.8% and 114.8% for all concentrations above LLOQ for all analytes. Within-run and between-run imprecisions were <7.6% for all concentrations above LLOQ. Plasma samples were stable at room temperature for 72 hours.
In DBS within-run and between-run accuracy were between 85.0% and 115% for all concentrations above LLOQ for all analytes, within-run and between-run imprecision were <15% for all concentrations above LLOQ. The extraction efficiency was greater than 95,4% with a relative standard deviation <5%. The spot-to-spot carry over was < 5%.
Plasma concentrations calculated based on DBS concentrations and corrected for hematocrit deviated <30% from observed plasma concentrations.

Conclusions:
The presented method enables simultaneous quantification of IVA, TEZ and ELX and its respective metabolites in plasma and DBS. In future studies, the developed methods can be applied for assessment of pharmacokinetics of new CFTR modulators in clinical routine and studies.

Towards precision dosing in psychiatry: population pharmacokinetics meta modelling of clozapine and lithium.

Aurélie Lereclus[1,2], Sylvain Benito[2], Raoul Belzeaux[4], Olivier Blin[1,3], Frédéric Dayan[2], Théo Korchia[5], Julien Welzel[2], Romain Guilhaumou[1,3]
[1]Aix-marseille Université, , France, [2]Exactcure, , France, [3]Service de Pharmacologie clinique et Pharmacovigilance, Hôpital de la Timone, , France, [4]Aix-Marseille Univ, AP-HM, CNRS, INT, Inst Neurosci Timone, Hôpital Sainte Marguerite, Pôle de psychiatrie, , France, [5]Département de psychiatrie, Sainte Marguerite University Hospital, Assistance Publique- Hôpitaux de Marseille, , France

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Background: Psychiatry is a critical area for treatment optimization. Molecules such as clozapine and lithium, which have a narrow therapeutic range and present significant inter- intra- variability in their pharmacokinetics require therapeutic drug monitoring (TDM) and treatment individualization. The use of population pharmacokinetics (popPK) models has the potential to improve therapeutic approaches through Model Informed Precision Dosing (MIPD). However, selecting the right model is challenging, as previously described for clozapine1. To improve the range of applicability of those models, meta modelling (MM) is especially adapted. Indeed, this methodology allows the combination of several popPK models to provide a better model including all significant covariates, and therefore improving the predictability on all subpopulations of interest2.
The aims of this study were to develop popPK meta models of clozapine and lithium and to assess their predictability in external datasets.
Methods: After external evaluation of all available popPK models of clozapine and lithium, three popPK models of clozapine and two popPK models of lithium were retained for this study. For clozapine, the model with the best fit and gender as a covariate was retained, in addition to two models with smoking status as a covariate, as we found a lack of predictability of the best model on non-smokers population. For lithium, the model with the best fit and fat free mass (FFM) as a covariate was retained, in addition to a model with good predictive performances and glomerular filtration rate (GFR) as a covariate, as lithium elimination is renal. Using innovative methods developed within Exactcure, under patenting process, we developed two meta models that included the most significant covariates for the molecules.
Results: Both meta models showed improved predictability compared to the original models. Clozapine meta model was a good predictor on the population level (MDPE(%): -0.1, MADPE(%): 27.4), as well on all subpopulations of interest (smokers : MDPE(%): 0.1, MADPE(%): 22.8; non-smokers :MDPE(%): -1.5, MADPE(%): 28.9; females : , MDPE(%): 0.3, MADPE(%): 22.5 rand males: MDPE(%): -0.8, MADPE(%): 27.4)). Lithium meta model met the acceptability criteria after external evaluation (MDPE(%): 0.7, MADPE(%): 26.7) and allowed the integration of renal status as a covariate for elimination parameterization.
Conclusion: Both meta models displayed significantly decreased biases and met the acceptability criteria for use in clinical practice on all subpopulations of interest. They both displayed more accurate predictions than the single models. Those models could be used in the perspective of MIPD for clozapine and lithium. Simulations of those models could increase the accuracy of precision dose calculations and provide therefore dosing guidelines for the subpopulations of interest.

Practices, Knowledge, and Attitudes of Nephrologists Towards Prescribing and Monitoring Vancomycin at Dialysis Centers

Dr Sarah Alghanem[1]
[1]College of Pharmacy at Kuwait University, , Kuwait

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction: Vancomycin has an important role in treating serious MRSA infections, hence optimal dosing is important, particularly in high-risk populations, such as those undergoing dialysis. However, vancomycin dosing protocols are varied in the literature for haemodialysis patients. This study sought to determine nephrologists' practices, knowledge, attitudes, and barriers toward prescribing and monitoring vancomycin at dialysis centers.
Materials and Methods: A cross-sectional and multi-center study was conducted in Kuwait using a validated self-administered questionnaire among 168 nephrologists. Descriptive and comparative analyses were performed using SPSS (version 28).
Results: The response rate was 75% (n=126). Over half of nephrologists frequently prescribed a vancomycin loading dose of 1000mg (53.2%) and a maintenance dose of 500mg (51.6%) to all patients. Their overall median (IQR) percentage knowledge about the therapeutic monitoring of vancomycin was 66.7% (33.3) and was found to be higher in nephrologists aged ?40 years and in registrars/senior registrars ($p<0.05$). Their overall median (IQR) attitude score was 4.0 (1.0) [positive attitude]. Nephrologists with >15 years of practice experience expressed higher attitudes ($p<0.05$). The top two perceived barriers were a lack of clear local hospital/ national guidelines (60.3%) and inconsistencies among different dosing references and guidelines (51.6%).
Discussions and Conclusions: Findings showed that nephrologists have varying practices, moderate knowledge, and positive attitudes towards prescribing and monitoring vancomycin and highlight the need for interventions to overcome the perceived barriers.

Ixekizumab Trough Concentrations in Psoriasis: Paving the Way towards Personalized Therapy - A Cohort Study

dr. Lisa Schots[1], dr. Rani Soenen[1], dr. Debby Thomas[2], dr. Erwin Dreesen[2], Prof. dr. Jo Lambert[1]
[1]Department of Dermatology, Ghent University Hospital, Ghent, Belgium, [2]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium, [3]3. Department of Dermatology, AZ Delta, Torhout, Belgium

Biologicals, Sal B, september 26, 2023, 13:00 - 14:30

Importance: Biologics for psoriasis (Pso) demonstrate varying clinical outcome in daily practice, implying potential under- and overexposure.
Objective: Primarily, to explore whether there is an exposure-response relationship of ixekizumab (IXE) in Pso patients. Secondarily, to develop and validate an IXE in-house sandwich-type enzyme-linked immunosorbent assay (ELISA), and to evaluate whether patient factors influence IXE exposure and clinical outcome.
Design: Prospective, real-world cohort study (BIOLOPTIM-IXE) between 2020 and 2022.
Setting: Multicenter study recruiting from two referral centers: the Departments of Dermatology of the Ghent University Hospital and AZ Delta Torhout, Belgium.
Participants: Adult Pso patients treated with IXE according to standard dosing regimen.
Exposure(s): IXE, 80 mg every 4 weeks.
Main Outcome(s) and Measure(s): Clinical outcomes: absolute Psoriasis Area and Severity Index (PASI) and PASI reduction from baseline (ΔPASI). Optimal and suboptimal clinical response were defined as absolute PASI ≤ 2 or ΔPASI ≥ 90, and absolute PASI > 2 or ΔPASI < 90, respectively. Biochemical measures: IXE serum trough concentrations (TCs).
Results: Using MA-IXE117E12 and MA-IXE100F5-biotin as the capture and detection antibodies, respectively, an ELISA was developed with a exposure-responsecurve ranging from 10 ng/mL to 0.16525 ng/mL. One hundred fifteen serum samples collected throughout steady-state (≥ 22 weeks of treatment) from 48 patients (19 [39.6%] female; median age, 46.5 [range, 36.5-60.0] years) were included. Median cohort IXE TC was 4.1 [2.8-6.1] µg/mL. Patients with optimal response (PASI ≤ 2) had significantly higher TCs than subjects with suboptimal response (PASI > 2) (median TCs, 4.4 µg/mL and 3.0 µg/mL, respectively; P = 0.026). A minimal effective steady-state IXE TC of 3.4 µg/mL was identified for clinical outcome defined by absolute PASI. Median TCs and absolute PASI were significantly lower and worse, respectively, in patients ≥ 90 kg (P < 0.001 and P = 0.013, respectively) and in biologic experienced subjects (P < 0.001 and P = 0.029, respectively).
Conclusions and Relevance: These results suggest an IXE exposure-response relationship in real-world, adult Pso patients, and propose a minimal effective steady-state TC of 3.4 µg/mL, revealing the potential role of therapeutic drug monitoring in optimizing IXE use.

Dried blood spot (DBS) analysis of immunosuppressants: a more sustainable way to monitor patients after renal transplantation

MSc Robin Weijland[1,3], PhD Naomi Van der Linden[2], Professor Ruud Verdaasdonk[3], PhD, PharmD Dina Kweekel[1]
[1]Leiden University Medical Center, Leiden, the Netherlands, [2]TU Delft, Institute for Health Systems Science, Delft, the Netherlands, [3]University of Twente, TechMed Center, Enschede, the Netherlands

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Background
Renal transplant patients are treated with immunosuppressing drugs to prevent organ rejection. These drugs need to be titrated to the right dose, since high levels are toxic and low levels pose an increased risk of rejection. To do this, frequent blood sampling and concentration measurements are necessary, which is called therapeutic drug monitoring (TDM). Traditionally, the drugs (such as tacrolimus, everolimus, ciclosporin and mycophenolic acid) are measured in plasma or blood ("traditional TDM"). In the Leiden University Medical Center (LUMC) an area under the curve is calculated for each drug using multiple samples taken over the course of several hours. This method implies a long waiting time in the hospital for patients. A novel alternative, "DBS-sampling", allows for the patients to draw blood themselves, at home, and send the samples by mail to the laboratory. Although patient convenience has been investigated for DBS-sampling, costs and environmental sustainability of DBS-sampling (as compared to traditional TDM) have not been studied in detail yet.

Methods
A probabilistic cost-effectiveness analysis was performed to compare the costs and carbon emissions between the two sampling strategies, using 1000 simulations over a 15-year time horizon. Data from patients after kidney transplantation (n=1097) was obtained from the LUMC, including the number and type of analyses, using either DBS-sampling or traditional TDM. Other data sources included interviews with nephrology department staff, observing analytical and laboratory personnel, previous literature, web sources, and protocol review to determine the resource use for blood sampling and analysis. Costs were calculated for the analyses, productivity loss, labor, energy use, transport and waste handling, with a 4% discount rate. Outcomes included Net Monetary Benefit and disability-adjusted life years (DALYs) due to carbon emissions. The latter captures environmental impact on health, is commonly used in economic evaluations and can therefore be compared between studies.

Results
Patient travel (to the hospital) had the largest share of overall carbon emissions for both sampling strategies, followed by energy consumption. Labor costs were the main contributor to overall costs for traditional TDM and DBS-sampling, followed by patient productivity loss.
Overall savings when using DBS-sampling instead of traditional TDM amounted to € 1,6M and 0.0209 averted DALYs (16,090kg CO_2) calculated over 1000 patients in a 15-year period. This amounts to on average € 108,- per patient per year. Productivity loss was lower for patients using DBS-sampling.

Conclusions
This study suggests DBS-sampling results in lower costs and lower carbon emissions compared to traditional TDM. Most costs are saved due to less productivity losses as patients don't have to wait in the hospital. Carbon emissions are lower mainly because less energy is needed for the DBS analysis. Lastly, since DBS-sampling can be performed at home, visiting the hospital for blood sampling is no longer necessary. If these patients could receive online doctor consultations, this would further increase savings in patient transportation and overall carbon emissions. Study limitations are that some data may not be applicable to other hospitals, and that environmental impact beyond carbon emissions is not included.

Population pharmacokinetics of lenalidomide in Chinese patients with B-cell malignancies

Dr. Yi Ma[1], Mr. Zaiwei Song[1], Mr. Hao Bing[1,2], Mr. Huan He[2], Prof. Libo Zhao[1], Prof. Rongsheng Zhao[1]
[1]Peking University Third Hospital, , China, [2]Beijing Children's Hospital, , China

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction: Currently, lenalidomide has been widely used in the treatment of various hematological malignancies. Dose-dependent adverse events of lenalidomide have been reported previously, and thus there is a clinical need for proper dose modifications to manage toxicities. Establishing a precise and predictable population pharmacokinetic (PopPK) model is a key step to achieve dose individualization, whereas PopPK model of lenalidomide in Asian populations is still lacking. The aim of this study was to conduct a PopPK analysis of lenalidomide in Chinese patients with B-cell malignancies to support the dose individualization.

Materials and Methods: A total of 164 plasma concentration of lenalidomide from 97 patients at four centers with multiple myeloma (MM) and B-cell non-Hodgkin lymphoma (NHL) was included. The plasma concentration of lenalidomide (daily dose of 10-25mg) were detected by was determined by a validated LC-MS/MS method. PopPK models were developed in Phoenix 8.3 (Certara USA Inc., Princeton, NJ, USA) using a non-linear mixed effects model (NLME), and descriptive statistical analysis of the data was implemented using SPSS 26 (IBM Ltd, USA). Both internal and external methods were used for final model validation.

Results: A one-compartment model with first-order elimination best described the pharmacokinetics of lenalidomide, with appropriate goodness of fit. The population typical values of lenalidomide were as follow: absorption rate constant (Ka) of 1.10 h-1, apparent volume of distribution (Vd) of 27.4 L, and apparent clearance (CL) of 6.1 L/h. Covariate analysis indicated that the creatinine clearance (CCr) and body surface area (BSA) correlated with CL and Vd, respectively. Cancer type (NHL or MM), sex, age, liver function and other demographics or clinical characteristic had no significant effect on the model. The external validation results showed that the concentrations predicted by Bayesian feedback were close to the observed values, with a mean absolute percentage error (MAPE) of 2.9%, which was significantly lower than previously published Connarn model (MAPE: 65.3%) and Hughes model (MAPE: 22.7%).

Discussions and Conclusion: This the first report of lenalidomide PopPK model using data from Chinese patients in real clinical settings. We demonstrated that the CCr and BSA are key factors to evaluate lenalidomide disposition in Chinese patients. This model has potential to improve the personalized treatment of lenalidomide in Chinese patients with NHL or MM.

Quantification of four CFTR-modulators in plasma and breastmilk by LC-HRMS

MScEng Anna Hansson[1], MD, PhD Hjalmar Wadström[1,3], Sara Bildsten[1], Gry Öyerhavn[1], PhD Victoria Barclay[1,2], MD, PhD Erik Eliasson[1,2]
[1]Medical Unit for Clinical Pharmacology, Karolinska University Hospital, Stockholm, Sweden, [2]Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Institute, Stockholm, Sweden, [3]Clinical Epidemiology Division, Karolinska Institutet, Stockholm, Sweden

Miscellaneous 1, Møterom 2, september 26, 2023, 13:00 - 14:30

Introduction:
Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This results in the malfunction of ion and fluid transport and thickening of mucus. Stagnant thick mucus causes recurring infections and inflammation in the lungs with ensuing tissue damage and often other organs are affected. Until recently, the treatment of CF was symptomatic. However, in 2012 the first CFTR-modulator ivacaftor (IVA) which targets the underlying cause of the disease by restoring CFTR function was approved. In the following years other CFTR-modulators were approved including Trikafta which is a combination of three modulators elexacaftor (ELX), tezacaftor (TEZ) and ivacaftor in 2019.
Knowledge gaps concerning the pharmacokinetics and the toxicity of CFTR-modulators remain and they are also prone to drug-drug interactions. This makes them candidates for therapeutic drug monitoring (TDM). The main indications for TMD of CFTR-modulators in plasma samples is lack of response, adverse effects, and potential drug-drug interactions. The ability to also monitor the CFTR-modulators in breastmilk enables estimation of the exposure of the breastfed infant, with a potential concern for CFTR-modulator induced liver damage.
Method:
An analytical method for quantification of four CFTR-modulators, IVA, lumacaftor (LUM), TEZ and ELX in human plasma and breastmilk were developed and validated. The analysis was done on a Thermo Vanquish Flex Binary UHPLC system coupled to a high-resolution mass spectrometer (HRMS), Thermo Q Exactive (Thermo Fisher Scientific). The analytes were detected using positive electrospray ionisation with full scan mode. After sample preparation by protein precipitation, the supernatant was injected on to the LC-system and the analytes were separated using a Zorbax SB-C18 Rapid Res HPLC column (3.5µm, 4.6×75 mm, Agilent Technologies). The total chromatographic time was 3.75 minutes.
Results:
The method was validated according to European Medicines Agency guidelines. The acceptance criteria were fulfilled for accuracy,precision and robustness as well as qualitative and quantitative matrix effects within the quantification range of 0.005-10µg/mL for IVA and 0.05-100µg/mL for LUM, TEZ and ELX for both plasma and breastmilk.
The quantification of breastmilk can be done with a six-point calibration curve in plasma and there is little to no matrix effect between the two matrixes.
Discussion and conclusion:
A simple and sensitive LC-HRMS method for the simultaneous quantification of ivacaftor, lumacaftor, tezacaftor and elexacaftor in human plasma samples and breastmilk has been validated and is used in the routine TDM analysis of CFTR-modulators. During the last eight months 30 patient plasma samples and three breastmilk samples from breastfeeding mothers have been analysed at the TDM laboratory.

Development and validation of an LC-MS/MS method for quantification of total and unbound concentration of vancomycin

PhD Jennie Östervall[1,2], MD, PhD Erik Eliasson[1,2], PhD Victoria Barclay[1,2]
[1]Medical Unit for Clinical Pharmacology, Karolinska University Hospital, Stockholm, Sweden,
[2]Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Institute, Stockholm, Sweden

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction:
Vancomycin (VAN) is a glycopeptide antibiotic widely used for the treatment of infections caused by multi-resistant gram-positive bacteria, for example MRSA or KNS. Therapeutic drug monitoring (TDM) is necessary due to the risk of low concentrations leading to therapeutic failure or high concentrations causing nephrotoxicity. Laboratory monitoring of the free (non-protein bound) plasma concentration may help to guide individual dosage even further, especially in selected cases within intensive care where protein binding of antibiotics are known to vary extensively between patients. At the TDM laboratory at Karolinska University Hospital, the quantification of VAN is today performed by immunochemistry. This method can only be used for the determination of total concentrations in serum and EDTA-plasma. Therefore, the development of an LC-MS/MS method for the determination of total VAN in plasma/serum and unbound VAN (after ultrafiltration) was required.
Materials and Methods:
An LC-MS/MS method was developed and validated for the quantification of VAN in human plasma. The analysis was performed on an Acquity Ultra Performance LC-system I-class with a Xevo TQ-S micro mass spectrometer (Waters Ltd.) operating in positive mode with electrospray ionization. A Zorbax SB-Aq 2.1x50 mm 5 µm column (Agilent Technologies) was used for chromatographic separation using 0.1 % formic acid in water and acetonitrile as mobile phases with a flow rate of 0.6 mL/min. The total analysis time was 2.25 min. For the determination of total VAN, plasma was precipitated with acetonitrile containing a deuterated internal standard. After mixing and centrifugation, the supernatant was diluted with 0.1 % formic acid and injected onto the LC-system.
Results:
The total method was validated in the range of 1-75 µg/mL according to the ICH harmonized guideline, bioanalytical method for validation and study sample analysis M10. Accuracy and precision CVs were less than 15 % for all quality control levels. No differences in process efficiency were found for plasma (heparin, EDTA and citrate) and serum. The method showed acceptable agreement with the immunochemical method used at the laboratory today.
Discussions and Conclusions:
A fast and robust method with an easy sample preparation for the determination of total VAN was validated. The same instrument method will be able to be used for the quantification of the unbound concentration of vancomycin in plasma/serum.

Recommendations and quality of therapeutic drug monitoring guidelines in oncology: insights from a systematic review

Mr. Zaiwei Song[1], Ms. Xinya Li[1], Dr. Zhanmiao Yi[1], Mr. Jiguang Qin[1], Ms. Dan Jiang[1], Dr. Zhitong Wang[1], Mrs. Huibo Li[1], Prof. Rongsheng Zhao[1]
[1]Peking University Third Hospital, , China

Oncology, Møterom 2, september 25, 2023, 13:00 - 14:30

(1) Introduction: Compared to anti-infective drugs, immunosuppressants and other fields, the application of therapeutic drug monitoring (TDM) in oncology is somewhat limited. Herein, this systematic review aims to provide a comprehensive understanding of the overall situation and current recommendations as well as the quality evaluation of TDM guidelines in oncology and to promote the development of TDM in the field of oncology.

(2) Materials and Methods: Databases including PubMed, Embase, the official websites of TDM-related associations and Chinese databases (SinoMed, CNKI, and Wanfang Data) were comprehensively searched up to March 2023. Two investigators independently screened the literature based on the inclusion and exclusion criteria and extracted data according to the predesigned form. The methodological and reporting quality was evaluated using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) and the Reporting Items for Practice Guidelines in Healthcare (RIGHT), respectively. Recommendations and quality evaluation results were presented by visual plots. This study was registered in PROSPERO (No. CRD42022325661) and performed according to the PRISMA guidelines.

(3) Results: A total of eight studies were included, with publication years ranging from 2014 to 2022. From the perspective of guideline development, two guidelines were developed using evidence-based methods. Among the included guidelines, four guidelines were for cytotoxic antineoplastic drugs, three for small molecule kinase inhibitors, and one for antineoplastic bio-similars. For the TDM recommendations, chromatography-related analytical methods were most commonly recommended, and the area under the plasma concentration–time curve (AUC) was the most commonly used indicator. Currently available guidelines and clinical practice provided a complete process of individualized medication of antineoplastic drugs based on TDM, as well as influencing factors of TDM. With regard to methodological quality, the AGREE II evaluation showed that the domain of scope and purpose received the highest score (87.30%), and rigor of development received the lowest score (32.29%). The average overall quality score was 55.21%. With regard to the reporting quality by RIGHT evaluation, the average reporting rates in review and quality assurance (37.50%) and funding, declaration and management of interests (21.88%) were lower compared with basic information (70.83%), background (60.94%) and other information (79.17%).

(4) Discussions and Conclusions: From the perspective of current guidelines, TDM in oncology is now being expanded from cytotoxic drugs to newer targeted treatments. Whereas, the types of antineoplastic drugs involved are still small, and there is still room for improvement in the quality of TDM guidelines for antineoplastic drugs. Furthermore, the reflected gaps warrant future studies into the exposure-response relationship and pharmacokinetic models to further support individualized therapy.

Validation of a LC-MS/MS method for quantification of Ampicillin in plasma

Ph.d Simon Sjödin[1], Ph.d Mattias Tranberg, Torleif Jonsson, MD, Ph.d Magnus Axelsson
[1]Sahlgrenska University Hospital, , Sweden

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction
Ampicillin is an antibiotic belonging to the group of beta-lactams used against serious infections in intensive care settings. Effective treatment requires maintaining adequate concentration while avoiding adverse events. Thus, assessing the concentration of ampicillin in relation to the minimum inhibitory concentration is important. Here we have validated a LC-MS/MS method for quantification of the concentration of ampicillin in plasma.
Materials and Methods
A stock solution of ampicillin was used for creating a calibration curve with 0.10, 1.0, 10, 50 and 100 mg/L ampicillin, as well as quality controls samples at 0,10, 1.0, 25, 75 and 500 mg/L. Ampicillin-D5 was used as an internal standard. Samples were prepared by protein precipitation followed by phospholipid removal and dilution in H2O before analysis. The samples were analyzed by LC-MS/MS using a XEVO TQ-S (Waters). Chromatographic sample separation was performed in reversed phase and data acquisition was made in multiple reaction monitoring mode.
The validation experiments included calibration curve, accuracy, precision, dilution integrity, matrix effects, LLOQ, carry-over, stability of processed samples, and recovery. Calibration and linearity were investigated by analyzing the calibration curve on five occasions. The precision was investigated at 0.10-75 mg/L by analyzing five replicates on three occasions. Dilution was investigated by serial dilution 500 mg/L down to 0.032 mg/L as well as by diluting processed sample ten times in H2O. Matrix effects were investigated by spiking six extracted plasma samples or extracted H2O with 0.10, 3.0 or 400 mg/L ampicillin prior to analysis. Carry-over was investigated by analyzing blank plasma following injection of a 100 or 500 mg/L sample. Stability of processed sample was investigated after 24 and 72 h at +10°C. Finally, recovery was investigated by analyzing the difference in concentration between six samples with 1.0 mg/L ampicillin spiked further to a total concentration of 5.0 mg/L.
Results
The calibration curves showed residuals <5% for all concentrations including LLOQ. The intermediate repeatability was <8.0% in the concentration range of 0.10-75 mg/L. Serial dilution of 500 mg/L was acceptable down to 0.032 mg/L with a bias ≤7.5%. Similarly, processed sample at 500 mg/L could be diluted ten times in H2O with a bias of −0.17%. Matrix effects at 0.1, 3.0 or 400 mg/L had an internal standard normalized matrix factor of ≥0.98. Carry-over following an injection of 500 mg/L was 0.003% of measured area, corresponding to 11% of LLOQ. Processed samples, at 1.0 and 25 mg/L, were stored in the autosampler at +10°C for 24 and 72 h and deviated no more than 7.0%. The recovery between 1.0 and 5.0 mg/L was 105%.
Discussions and Conclusion
We have developed and validated a LC-MS/MS method for therapeutic drug monitoring of ampicillin in plasma. The validation included assessing the calibration curve, accuracy, precision, dilution integrity, matrix effect, LLOQ, carry-over, stability of processed samples, and recovery, all of which fulfilled our predetermined criteria. The method has a measurement interval of 0.01-100 mg/L and a precision <8.0%. The method is currently being used for monitoring plasma concentration of ampicillin in clinical studies.

DOSE OPTIMIZATION BY A CLINICAL DECISION SUPPORT SYSTEM OF VANCOMYCIN IN (MORBID) OBESE PATIENTS

Dr Lisanne Krens[1], Tessa Bosch[1], Lavina de Visser[1], Lieke Mitrov[1]
[1]Maasstad Ziekenhuis, , Netherlands

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction
Obese patients treated with vancomycin may need a higher dosing regimen to achieve therapeutic drug levels. In the Maasstad and Ikazia hospital the recommended starting dose in obese patients is 30 mg/kg/day. We developed a Clinical Decision Support System (CDSS) for (morbid) obese patient using vancomycin, to alert the pharmacist of incorrect dosing. The system generate as rule when less then 30 mg/kg/day is prescribed. The aim of this study was to determine if the use of CDSS of vancomycin would lead to attaining vancomycin target levels quicker.

Materials and Methods
During this retrospective pre- post intervention study a total of 100 patients were included. Patients were included when they were ≥ 18 years, received vancomycin IV and had a BMI ≥ 35 and/or TBW ≥ 100 kg. The Control (CTRL)-group were compared to the clinical rule (CR)-group. Primary outcome is time until therapeutic vancomycin target level. For primary outcome measure, Kaplan-Meier (K-M) and Cox proportional hazard models were used to assess difference in time to therapeutic vancomycin target level.

Results
In total 100 patients were included, 55 CTRL and 45 CR. In total 69 patients reached a therapeutic vancomycin target level, 32 (71%) in the CR and 38 (69%) in the CTRL-group. In the CR group, the median was 3 days for 50% of the patients to reach therapeutic target level and 3,5 days for the CTRL-group (not significant).
In the CR-group 24 times action was taken by the pharmacist. No action was taken in 12 cases (30%) when needed according to the clinical rule. This resulted in incorrect dose at start of vancomycin therapy. Besides in 17 of 45 cases no correct starting dose of 30 mg/kg/day was given, nevertheless the standard dose of 2dd1000mg was prescribed. The median time to initial target level between the CR-group and the CRTR-group was 2.6 days vs. 1.9 days.

Discussions and Conclusions
Implementing a CDSS for vancomycin in (morbid) obese patients did not have impact on the time until therapeutic vancomycin target levels were reached between the control and intervention group. When the clinical rule was generated, most patients already received the first dose of vancomycine. In some cases also vancomycin level were already ordered by the physician. In those cases, an incorrect dose was accepted by the pharmacist. We observed a lack of intervention by the pharmacist, caused by a “wait and see” attitude for the first blood vancomycin level was known. This observation endorses the importance to evaluate the use of a CDSS in real life practice in order to optimize the system and to improve obese patients response on vancomycin therapy.

Preeclampsia may indicate increased maternal exposure to betamethasone in pregnancy: a population pharmacokinetic study

Mr Letao Li[1], Dr. Sam Schoenmakers[2], prof. dr. Irwin Reiss[3], Prof. Karel Allegaert[8], Dr. Sjoerd van den Berg[4], Mr Bertrand Van Zelst[4], Prof. Dr. Ron van Schaik[5], Dr. Philip DeKoninck[2], Ms Emma Ronde[2], Dr. Sebastiaan Sassen[1], Dr. Sinno Simons[3], Prof. Dr. Birgit Koch[1]
[1]Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, Netherlands, [2]Department of Obstetrics and Gynaecology, Rotterdam, Netherlands, [3]Department of Pediatrics, Division of Neonatology, Rotterdam, Netherlands, [4]Department of Internal Medicine, Division of Endocrinology, Erasmus University Medical Center, Rotterdam, Netherlands, [5]Department of Clinical Chemistry, Erasmus University Medical Center, Rotterdam, Netherlands, [6]Center for Antimicrobial Treatment Optimization Rotterdam (CATOR), , Netherlands, [7]Rotterdam Clinical Pharmacometrics Group, the Netherlands, , Netherlands, [8]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium, [9]Department of Development and Regeneration, KU Leuven, Leuven, Belgium, [10]Leuven Child and Youth Institute, KU Leuven, , Belgium

Miscellaneous 1, Møterom 2, september 26, 2023, 13:00 - 14:30

Abstract: Maternal dosing of antenatal corticosteroids (ACS) to improve fetal lung development in case of imminent preterm birth has remained the same "one dose fits all" for years, although dosing is not optimal based on side effects and efficacy. The first step to improve ACS dosing is to understand factors that influence maternal exposure. Therefore, we established a betame-thasone population pharmacokinetic model in pregnant women. Prospective single center pharmacokinetic study in women admitted for imminent preterm birth (23+5 - 33+6 weeks of gestation) treated with intramuscular betamethasone (2 doses, 12 mg once daily). Population pharmacokinetic modelling was performed using Non-linear mixed effects models (NONMEM). 194 blood samples from 28 patients (23 healthy, 5 preeclampsia) were collected and analyzed. The model was best described using a two-compartment model. The population mean estimate for absorption constants, central volume distribution, peripheral distribution volume, clearance and half-life for an average patient were 1.7 h-1, 46.1L, 109L, 14.4 L/h and 7.4h, respectively. Be-tamethasone clearance in preeclamptic women was 40% lower compared with non-preeclamptic women (9.35 versus 15.78 L/h) resulting in a 40% median increase in betamethasone exposure (1567 versus 1114 ng.h/ml). The study suggests a significant dose reduction of betamethasone may be needed in preeclampsia.

Drug-drug interaction between isavuconazole and tacrolimus in solid organ transplant recipients, which magnitude in clinical practice?

Diane Le Bouedec[1], PharmD, PhD Benedicte Franck[1], PharmD Christelle Boglione-Kerrien[1], PharmD, PhD Marie-Clémence Verdier[1], PharmD, PhD Florian Lemaitre[1], Dr Camille Tron[1]
[1]Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail)-UMR_S 1085, Rennes, France

Immunosuppression 2, Sal D, september 26, 2023, 13:00 - 14:30

Introduction:Isavuconazole (ISV) is a triazole antifungal drug used against invasive fungal infections. In solid organ transplant recipients (SOT), triazoles are known to be perpetrators of drug-drug interaction (DDI) with tacrolimus by inhibition of CYP3A4/5, but ISV is expected to be a less potent inhibitor than the other azoles. Conflicting results have been reported regarding the dose reduction of tacrolimus to apply in case of co-administration with ISV [1]. The aim of this study was to describe the real-life DDI between tacrolimus and ISV in SOT recipients.

Material and methods:A retrospective monocentric analysis was performed in patients treated by tacrolimus in whom ISV was introduced. The following parameters were collected: type of transplantation, trough concentration (C0) of ISV, C0 and dose of tacrolimus before and after (at steady state) ISV initiation. Patients tacrolimus C0/dose ratios were compared before and after starting of the antifungal.

Results:A total of 14 SOT patients that started ISV between June 2020 and September 2022 were included in the analysis and were distributed as follow: 64% liver transplants recipients (TRs), 22 % kidney TRs, 7% heart TRs, 7% lung TRs.The median change in Tacrolimus C0/dose ratio after introduction of ISV was 48.8% (ranged from -13.6% to 714.8%). Tacrolimus C0/dose ratio was significantly higher after ISV introduction (p=0.03). No correlation was found between the variation of tacrolimus C0/dose and ISV C0.

Discussion / Conclusion:A moderate increase of tacrolimus exposure was observed after introduction of ISV suggesting that it is less prompt to interact with CYP3A4/5 substrates than other triazoles, although a large inter-patient variability of the magnitude of the DDI was observed. These results confirm that anticipation of tacrolimus dose reduction to manage DDI may be challenging. A cautious decrease in drug dosage (-25/-30%) can be considered when initiating ISV but should be combined with tacrolimus therapeutic drug monitoring to rapidly correct drug exposure imbalance.

[1] Rivosecchi RM et al. Effects of Isavuconazole on the Plasma Concentrations of Tacrolimus among Solid-Organ Transplant Patients. Antimicrob Agents Chemother. 2017 Aug 24;61(9):e00970-17 doi: 10.1128/AAC.00970-17

How antiretroviral therapy could be affected by physical activity, oxidative stress and genetics: a multidisciplinary pilot study in people with HIV.

Professor Jessica Cusato[1], Dr. ANNA MULASSO[2], MICOL FERRARA[3], GUIDO ACCARDO[4], ALICE PALERMITI[1], ALESSANDRA MANCA[1], MIRIAM ANTONUCCI[3], GIANLUCA BIANCO[1], DOMENICO MAIESE[1], FRANCESCO CHIARA[5], JACOPO MULA[1], ELISA DELIA DE VIVO[1], MARIA GRAZIA MADDALONE[1], MARIA CRISTINA TETTONI[3], SIMONE CUOMO[2], LETIZIA MARINARO[3], STEFANO BONORA[4], GIOVANNI DI PERRI[4], CORRADO LUPO[2], ALBERTO RAINOLDI[2], ANTONIO D'AVOLIO[1]
[1]University of Turin, Department of Medical Sciences, TURIN, Italy, [2]Department of Medical Sciences, NeuroMuscolarFunction | Research Group, University of Turin, TURIN, ITALY, [3]ASL Città di Torino, Amedeo di Savoia Hospital, TURIN, ITALY, [4] Unit of Infectious Diseases, Department of Medical Sciences, University of Turin, Amedeo di Savoia Hospital, TURIN, ITALY, [5]Laboratory of Clinical Pharmacology S.Luigi A.O.U., Department of Clinical and Biological Sciences, University of Turin, REGIONE GONZOLE, ORBASSANO, ITALY

Miscellaneous 2, Møterom 5, september 26, 2023, 13:00 - 14:30

Introduction It is known, physical activity could increase the production of oxidative stress biomarkers, including reactive oxygen species, affecting the expression genes encoding drug transporters involved in antiretroviral drugs metabolism and excretion and, consequently, clinical outcome. On the other hand, high oxidative stress levels and antiretroviral therapy could impact on lipid and muscle metabolism in people with HIV.
Currently, no studies are present in the literature concerning the link between physical activity, oxidative stress and antiretroviral drug exposure. Therefore, aim of this study was to evaluate if some oxidative stress biomarkers, physical activity test evaluation are able to affect drug exposure in people living with HIV and switching from triple to dual antiretroviral therapy.
Materials and methods People living with HIV (without HCV or HBV co-infections) were evaluated at baseline (BL), while treated with three drugs, and 6 months after the switch to dual therapy. Their lifestyle habits (sedentary versus non-sedentary) were also analyzed. WHOQoL-brief questionnaire was considered for the quality of life assessment. Physical function was quantified using validated tools such as the Tapping test for dexterity and the Sit to Stand test for leg strength. Plasma and intracellular (PBMCs) anti HIV drug concentrations and mitochondrial and cytosol oxidative stress biomarkers levels were evaluated through liquid chromatography tandem mass spectrometry.
Results 30 patients (10 sedentary and 20 non-sedentary) were included in the study: median (interquartile range, IQR) age and body mass index were respectively 42 (34-48) years and 23.2 (21.9-25.3) Kg/m2. Weight and viral suppression were maintained after switch, whereas the following biomarkers resulted statistically changed when comparing triple versus dual anti-HIV therapy: mitochondrial cysteine, cytosol taurine, cytosol S-adenosilmethionine, AST (but within the normality ranges), calcium and vitamin D levels. Also dominant tapping test, sit to stand and physical pain resulted statistically different considering the switch.
Stratifying for physical activity, significant differences were suggested for cytosol N-formylmethionine, alkaline phosphatase and vitamin D levels for triple therapy, cytosol glutathione and hemoglobin for dual therapy, when comparing inactive versus physically active people living with HIV. Finally, demographic, genetic, oxidative stress biomarkers and physical activity-related factors were considered in a logistic regression analysis evaluating which variable were able to affect toxicity-associated drug concentrations: single nucleotide polymorphisms in PXR and CAR transcription factors encoding genes, body mass index, cytosol glutathione and tapping test resulted predictive factors.
Discussion and Conclusions For the first time, this study a possible link between oxidative stress biomarkers, physical activity and genetics in affecting drug exposure. Further studies in larger cohorts of patients are required in order to confirm these data.

Clozapine plasma concentrations in schizofrenic patients: a possible role of vitamin D related gene variants

Dr Alessandra Manca[1], Dr Alice Palermiti[1], Dr Jacopo Mula[1], Dr Miriam Antonucci[2], Dr Domenico Maiese[1], Dr Gianluca Bianco[1], Dr Elisa Delia De Vivo[1], Dr Flavio Vischia[3], Dr David De Cori[3], Dr Sara Venturello[4], Dr Guido Emanuelli[5], Prof Jessica Cusato[1], Prof Antonio D'Avolio[1]
[1]Laboratory of Clinical Pharmacology and Pharmacogenetics; Department of Medical Sciences, University of Turin, Amedeo di Savoia Hospital, Turin, Italy. , , , [2]SCDU Infectious Diseases, Amedeo di Savoia Hospital, ASL Città di Torino, 10149 Italy., , , [3]Department of Mental Health – Psychiatric Unit West Turin , Italy., , , [4]Department of Mental Health–Psychiatric Unit East, Day Service S.G. Bosco 10144-Turin, Italy., , , [5]Department of Mental Health–Psychiatric Unit East, S.G. Bosco 10144-Turin, Italy., ,

Psychiatry, Møterom 4, september 25, 2023, 13:00 - 14:30

Introduction
Treatment-resistant schizophrenia is associated with severe burden of disease, poor quality of life and functional impairment: clozapine (CLZ) is the most effective antipsychotic in drug-resistant patients.
Despite this, CLZ use in therapy is limited due to severe adverse effects such as agranulocytosis, cardiovascular arrest and seizures, which lead to poor compliance.
In the literature, many studies showed how psychiatric disorders could be associated with low vitamin D (VD); our group previously suggested that 57% of analyzed patients with mental disorders presented insufficient VD levels (10-30 ng/mL) and a possible role of VD in influencing CLZ plasma exposure.
CLZ showed important hepatic and extrahepatic metabolic variability, due to the differences in the expression of genes encoding enzymes involved in its biotransformation such as CYP1A2 and CYP2C19: these gene expression is modulated by VD.
Given all these considerations, aim of this study was to investigate if variants in genes encoding enzymes and transporters involved in CLZ biotransformation and polymorphisms related to VD pathway may influence CLZ drug concentrations, in order to identify VD-associated predictive factors useful for selecting patients with the highest probability of drug response and those more predisposed to toxicity.
Materials and Methods
Patients were enrolled at the Amedeo di Savoia and Giovanni Bosco Hospitals, Turin, Italy: drug concentration
analysis was conducted before the new dose assumption (Ctrough). CLZ and 25-OH-VD plasma concentrations were obtained through LC/MS-MS analysis.
CLZ therapeutic range was 350-600 ng/mL, and toxicity cut-off value was 1000 ng/mL.
DNA purification was realized starting from 200 µL of blood or plasma and allelic discrimination was assessed through the Real time- PCR.
The following allelic variants have been analysed: VDR ApaI C>A (rs7975232), VDR TaqI T>C (rs731236), VDR BsmI G>A (rs1544410), VDR FokI T>C (rs17535810), VDR Cdx2 A>G (rs11568820), VDBP GC1296 A>C (rs7041), CYP27B1 -1260 G>T (rs10877012), CYP24A1 3999 T>C (rs2248359), CYP24A1 8620 A>G (rs2585428), CYP27B1 +2838 C>T (rs4646536), CYP27A1 345 A>G (rs4674345), CYP2C8 681 C>T (rs1059681), CYP24A1 22776 C>T (rs927650), CYP1A2 -163 C>A (rs762551), CYP1A2 890 C>T (rs2470890) and CYP2C19*2 +681 G<A (rs4244285), ABCB1 3435 C>T rs1045642, ABCB1 1236 C>T (rs1128503), ABCB1 2677 G>T (rs2032582).
Results
150 patients were enrolled: median age was 48 years and median BMI was 27.1 (kg/m2).
All the analyzed polymorphisms resulted in Hardy Weinberg equilibrium, with the exception of CYP27B1 -1260 and CYP1A2 890. Median CLZ exposure was 419 ng/mL. Single nucleotide polymorphisms related to VD pathway resulted able to affect CLZ levels (VDR FokI p= 0.048 and

CYP27B1 +2838 p= 0.039), as for CYP1A2 -163 (p= 0.022). Demographic, hematochemical (VD) and pharmacogenetic factors were evaluated in logistic regression analyses considering the efficacy and toxicity cut-off values: for the 350 ng/mL cut-off, VD levels and VDR TaqI resulted predictive factors, whereas CYPA2 -163 for the 600 ng/mL cut-off and, finally, CYP27B1 and BMI resulted predictors of the 1000 ng/mL cut-off.

Discussion and conclusion

This is the first study showing a possible contribution of VD in terms of genetics in affecting CLZ levels, but further studies in larger cohorts are required.

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Fluconazole resistant urinary candidiasis: Can voriconazole be used as an alternative treatment?

Dr Christelle Boglione-Kerrien[1], Pr Jean-Pierre Gangneux[1], Dr Elodie Gautier-Veyret[2], Dr Thibaut Gelé[3], Dr Anne Hulin[3], Dr Sarah Baklouti[4], Dr Françoise Botterel[3], Dr Bénédicte Franck[1], Dr Sébastien Lalanne[1], Dr Camille Tron[1], Dr Fabrice Taïeb[1], Dr Marie-Clémence Verdier[1], Pr Eric Bellissant[1], Dr Florian Lemaitre[1]

[1]Rennes University Hospital, Rennes, France, [2]Grenoble Alpes Univeristy Hospital, Grenoble, France, [3]Henri Mondor University Hospital, Créteil, France, [4]IFB, Hôpital Purpan, Toulouse, France

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction:
Oral fluconazole is the treatment of choice for candiduria. However, a therapeutic alternative may be necessary in case of resistance of certain yeasts. The question arose whether voriconazole allows sufficient efficacy because this antifungal drug has a very low urinary excretion ≤ 1.5% of the dose [1]. The objective was therefore to assess the urinary exposure of voriconazole (VRZ) and its major metabolite, to study the opportunity of an alternative oral treatment for urinary candidiasis due to fluconazole-resistant yeast.

Material and methods:
A multicenter prospective study (Rennes-Créteil-Grenoble-Toulouse) included 15 patients treated with oral VRZ in order to study urinary diffusion. A validated liquid chromatography tandem mass spectrometry detection method was used to quantify VRZ and its main metabolite, N-oxide voriconazole (NOX), in urine and plasma from day 3 of the initiation of the treatment. The antifungal activity of VRZ and NOX was evaluated on different species of Candida.

Results:
Median urine concentrations (urine C°) were 1.7 µg/mL (range 0.5-5.9) and 27.7 µg/mL (range 9.0-71.1) for VRZ and NOX respectively, compared to median plasma concentrations, measured at 1.8 µg/mL (range 0.4-6.5) and 1.8 µg/mL (range 1.0-4.0) for VRZ and NOX respectively. The NOX antifungal activity, theoretically minimal, still needs to be quantified. The median % of VRZ detected in the urine was 0.8% of the initial dose, which is consistent with the literature [1]. If we focus on Candida glabrata, a species frequently resistant to fluconazole, VRZ urine exposure is a priori satisfactory for 75% of Candida glabrata at this concentration (median= 1.7 µg/mL) with PK/PD criterion VRZ urine C°> CMI, according to national sensitivity studies [2].

Discussion / Conclusion:
Voriconazole appears as a potential alternative to fluconazole in candiduria since it allows having a sufficient exposure for ¾ of Candida glabrata strains, despite its low diffusion in the urine.

QUANTIFYING THE EFFECT OF METHOTREXATE ON THE ADALIMUMAB RESPONSE IN PSORIASIS BY PHARMACOKINETIC-PHARMACODYNAMIC MODELLING

MD A.M. van Huizen[1], Paul Bank[2,3,4], MD, PhD1 G.E. van der Kraaij[1], MD A.H. Musters[1], MD, PhD C.I. Busard[1], MD, PhD S.P. Menting,[5], PhD T. Rispens,[6], PhD A. de Vries[7], MD, PhD M.B.A. van Doorn[8,9], MD, PhD E. Prens[8], MD, PhD J. Lambert[10], MD, PhD J.M.P.A. van den Reek[11], MD, PhD E.M.G.J. de Jong, PharmD, PhD R.A.A Mathôt, PharmD,[2], MD, PhD P.I. Spuls[1]
[1]Amsterdam UMC, Department of Dermatology, Amsterdam, The Netherlands, [2]Department of Hospital Pharmacy & Clinical Pharmacology, Amsterdam, The Netherlands, [3]NorthWest Clinics, Alkmaar, Netherlands, [4]Red Cross Hospital, Department of Hospital Pharmacy, Beverwijk, The Netherlands, [5]OLVG, Department of Dermatology, Amsterdam, The Netherlands, [6]Sanquin Research and Landsteiner Laboratory Academic Medical Center, Department of Blood Cell Research, Amsterdam, The Netherlands, [7]Sanquin Diagnostic Services, Amsterdam, The Netherlands, [8]Erasmus MC, Department of Dermatology, Rotterdam, The Netherlands, [9]Centre for Human Drug Research, Leiden, The Netherlands, [10]Ghent University Hospital, Department of Dermatology, Ghent, Belgium, [11]Radboud UMC, Department of Dermatology, Nijmegen, The Netherlands

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Background
The OPTIMAP trial showed that the combination of methotrexate (MTX) and adalimumab (ADL) treatment leads to less anti-drug antibodies (ADA) development. In this study,we quantified the pharmacokinetics (PK)/pharmacodynamics (PD) of ADL and evaluated the influence of MTX co-treatment.

Methods
A population PK-PD model was developed using a two-stage approach with prospective data from 59 psoriasis patients (baseline PASI score: 12.6) receiving ADL over 49 weeks. Typical PK and PD parameters and their corresponding inter-patient variability (IIV) were estimated. We performed a covariate analysis to assess whether IIV could be explained by addition of MTX and specific patient characteristics.

Results
In total, 330 PASI scores, 252 ADL serum concentrations and 247 ADA titers were available. A one-compartment model was used and resulted in an apparent volume of distribution (Vd/F) of 14.7 L/82 kg, an apparent clearance (CL/F) of 0.365 L/day/82 kg and an IIV on Cl of 31.8%. Presence of ADA (ADL group 46.7%, ADL+MTX group 38.7%; $p = 0.031$) increased CL/F ($p < 0.001$), e.g. an ADA level of 30 AU/ml increased CL/F with a factor of ~4.1. The relationship between ADL level and PASI was described with a turn-over inhibitory Emax model with an IC50 of 1.19 mg/L, a Kout of 0.0314 L/day and an IIV of 152.6%. In the PD model, a trend between a reduced IC50 and the concomitant use of MTX was detected ($p = 0.06$).

Discussion/Conclusion
Based on our PK-PD model, concomitant used MTX increases the clinical efficacy of ADL, through less ADA formation, a greater drug exposure and possibly via an additional clinical effect.

Predicting the Pharmacokinetics of Voriconazole in Patients with Cirrhosis and Supporting CYP2C19 Phenotype-Guided Dose Optimization by Physiologically Based Pharmacokinetic Modeling

Doctor Taotao Wang[1], Miss Jiaojiao Chen, Miss Sihan Li
[1]The First Affiliated Hospital Of Xi'an Jiaotong University, , China

Anti-infectives 2 - antibiotics and antifungals, Møterom 4, september 26, 2023, 13:00 - 14:30

Patients with liver cirrhosis are at a high risk of fungal infection. Voriconazole is widely used in the clinical treatment of fungal pathogens. However, the dosage regimen for patients with cirrhosis remains controversial.
This study aimed to develop a physiologically based pharmacokinetic (PBPK) model for optimizing dosage regimens. A PBPK model, integrating autoinhibition of cytochrome P450 3A4 (CYP3A4) and CYP2C19 gene polymorphisms, in healthy volunteers was developed and extrapolated to patients with cirrhosis in PK-Sim®, the final model was used to optimize dosage regimens based on the Child-Pugh classification and cytochrome P450 (CYP) 2C19 phenotypes, including CYP2C19 rapid metabolizer (RM), normal metabolizer (NM), immediate metabolizer (IM), and poor metabolizer (PM). Dose optimization was assessed to rapidly reach the steady-state concentration and maintain Cmin within the therapeutic window of 1–5 mg/L at steady-state.
Finally, the optimized PBPK model predictions showed good agreement with the clinical observations, with most observed concentrations falling within the 2.5% and 97.5% prediction intervals. For the collected test datasets, 89% of AUC ratios and 91% Cmax ratios were within 0.5- to 2.0-fold. The simulated results of the PBPK model indicate that, except for Child-Pugh class A RMs required a standard loading dose of 400 mg/12 hours for one day, a 50% of standard loading dose (200 mg/12 hours for one day) can rapidly reach the steady-state concentration for the other subgroups. For Child-Pugh class A and B RMs, 100–225% and 25–75% increases of the recommended maintenance dose (100 mg/12 hours) were required, respectively, to maintain the clinical efficacy of voriconazole. Once daily dosage regimen was not appropriate for Child-Pugh class A and B RMs due to the Cmin of voriconazole at the highest maintenance doses (400 mg/24 hours for Child-Pugh class A RMs and 200 mg/24 hours for Child-Pugh class B RMs) have not yet reached the minimum effective concentration of 1 mg/L. The standard maintenance dose was only appropriate for Child-Pugh class A and B NMs/IMs, Child-Pugh class A PMs, and Child-Pugh class C RMs. For Child-Pugh class B PMs, Child-Pugh class C NMs, IMs, and PMs, lower doses were required to avoid toxicity. With dose reduction of 25–50% for Child-Pugh class B PMs and Child-Pugh class C NMs, dose reduction of 50–75% for Child-Pugh class C IMs/PMs.
The PBPK simulations suggested that the Child-Pugh classification and CYP2C19 phenotypes are essential factors in determining the voriconazole dosage regimens in patients with liver cirrhosis.

Real-time inhalants particle emission monitoring for non-invasive prediction of lung deposition

Dr Daiki Hira[1], Ms Sakiko Hatazoe[2], Dr Tetsuri Kondo[3], Dr Satoshi Ueshima[2], Dr Tomonobu Okano[2], Dr Mikio Kakumoto[2], Dr Tomohiro Terada[1]
[1]Department of Clinical Pharmacology and Therapeutics, Kyoto University Hospital, Kyoto, Japan, [2]College of Pharmaceutical Sciences, Ritsumeikan University, Kusatsu, Japan, [3]Department of Respiratory Medicine, Shonan Fujisawa Tokushukai Hospital, Fujisawa, Japan

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

[Introduction] Inhalation therapy is the first choice for the treatment of respiratory diseases. Whereas, the lung deposition of inhalants is widely variable depending on the patient's respiratory function and inhalation pattern, leading to individual variability in therapeutic efficacy. Clinical utility of therapeutic drug monitoring for blood inhalant concentration remains controversial¹⁾. Therefore, alternative sampling strategy for lung inhalant deposition monitoring is desired. In the present study, the photo reflection method (PRM)^{2,3)} for detection of drug release via dry powder inhaler was constructed to evaluate the relationship between the particle emission signals and lung deposition profiles.
[Materials and Methods] The lung deposition of the inhaled drug from Symbicort® Turbuhaler® was evaluated using the Andersen cascade impactor (ACI), an in vitro aerodynamic particle size analyzer. Four different inhalation patterns were defined based on the flow increase rate (quick, mild, and slow) and peak flow rate (30 L/min and 60 L/min). The inhalation flow rate and particle emission profile were measured using an inhalation flow meter and a photo reflection drug release detector, respectively. The budesonide amount at each ACI stage was determined by the HPLC-UV method. As indices of lung deposition, fine particle fraction (FPF, %) were calculated. A time integration values of a product of the flow rate and the output by photo reflection (AUCFR-PE) was calculated as an index of particle emission.
[Results] The particle emissions generated by four different inhalation patterns were completed within 0.3 seconds after the start of inhalation, but were observed as a sharper and larger peak under conditions of higher flow increase rate. Additionally, under the slow flow increase rate condition, the particle emission signal was completed before reaching the defined peak flow rate. These were significantly correlated between the lung deposition (FPF) and the photo reflection signal AUCFR-PE (R²=0.740, P<0.01).
[Discussions] In general, higher flow rate condition leads to higher deagglomeration efficiency for dry powder due to stronger shear stress. While previous studies have reported that peak flow rate is an indicator of lung deposition, the peak flow rate could be an inappropriate indicator in the case of the slow flow increase rate.
[Conclusion] The particle emission signal by PRM could be a useful non-invasive real-time monitoring tool for dry powder inhalers.
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Coadministration of voriconazole and rifabutin may increase the risk of adverse drug reactions in patients with multiple infections

MD Yoonjin Kim[1], MD Sungyeun Bae[1], MD, Ph.D Youngran Yoon[2], MD, Ph.D Jaeseong Oh[1], MD, Ph.D Injin Jang[1]
[1]Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea, [2]Kyungpook National University School of Medicine, Daegu, Republic of Korea

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction
Co-infection of tuberculosis (TB) or non-tuberculous mycobacteria (NTM) with aspergillus poses a challenge in medication selection due to significant drug interactions between rifamycins and azole antifungals. Voriconazole, an azole antifungal drug, is mainly metabolized by the hepatic cytochrome P450 (CYP) enzymes CYP2C19, CYP2C9, and CYP3A4. Rifampin, the most commonly prescribed rifamycin, is a potent inducer of the CYP enzymes, resulting in a significant decrease in the serum concentration of voriconazole. Some researchers suggested rifabutin use as an alternative to a rifampin due to its lower potency in inducing the CYP enzymes, although it is also contraindicated in drug label. This study presents clinical cases of voriconazole and rifabutin co-administrations and its potential risks were evaluated.

Material and Methods
A retrospective study was performed using clinical data retrieved from Seoul National University Hospital Patients Research Environment system. Patients who met the following criteria were identified: (1) admitted to the Seoul National University Hospital between January 2013 and December 2022, (2) received rifabutin in combination with voriconazole, and (3) had their serum concentration of voriconazole measured at least two times. The serum concentration of voriconazole was evaluated to evaluate the enzyme induction effect of rifabutin. Laboratory results, vital signs, electrocardiograms, and other medical records were reviewed to evaluate the safety of co-administaration of rifabutin and voriconazole.

Results
Three cases, including 2 males and 1 female, aged between 57-84, met the aforementioned criteria. In order to achieve therapeutic levels of voriconazole (1.0-5.5 mg/L), it was necessary to administer 2-2.5 times higher doses than those recommended in the FDA label due to the CYP induction caused by rifabutin. However, before reaching the therapeutic concentration, patients experienced various adverse effects: One experienced exacerbated nausea, vomiting, and first-onset tonic-clonic movement and the others exhibited prolonged QT intervals (QTcF 480-500). Additionally, due to their poor medical conditions, the patients experienced recurrent pneumonia, which led to septic shock, and soon after that, the voriconazole level dramatically increased. Ultimately, all three patients experienced either visual or auditory hallucinations, which led to the discontinuation or a change in their antifungal medication.

Discussions and Conclusion
The findings of the study have revealed potential drug interactions between rifabutin and voriconazole that pose significant risks to patients, including QT prolongation, exacerbated nausea, and visual/auditory hallucinations. The QT prolongation, a well-known adverse reaction of voriconazole, could be attributed to the co-administration of high-dose voriconazole with other drugs known to cause QT prolongation, such as azithromycin, amiodarone, and quetiapine. Furthermore, recent studies have shown that the inflammatory status of patients can significantly impact the metabolism and serum concentration of voriconazole. Patients at high risk of septic shock might have a higher voriconazole level, resulting in severe adverse events, like hallucinations. Therefore,

clinicians should exercise caution and closely monitor patients for adverse events when considering the use of rifabutin as a substitute for rifampin.

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24/7 fully automated therapeutic drug analysis by LC/MS/MS

Mrs Aurore Jaffuel[1], Dr. Frank Streit[2], Prof. Dr. Andreas Fischer[2], Kohei Yoshikawa
[1]Shimadzu Corporation Japan, Kyoto, Japan, [2]Department of Clinical Chemistry, University Medical Center Goettingen, Goettingen, Germany

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

1. Introduction

Simplifications in LCMS instrumentation have made MS a viable option for clinical research. This technique has the advantage of specificity, accuracy, and reduced reagent costs compared to immunoassays. The ability to support various analysis methods on a single system is a key feature. However, it is not always easy to quickly alternate between several different analytical methods. Also, automation is an essential function in aiming for a better quality of results and better comfort for the users in testing laboratories. However, lately, the automation of biological sample extraction, directly coupled to LCMS, has proven to be a challenge in the field.

A collaboration between the University Medical Center Göttingen (UMG) and Shimadzu Corporation was built to jointly develop and validate multiple analytical methods for therapeutic drugs, using a fully automated platform. The purpose is the development and the validation of a unified methods set for LCMS, for 24/7 therapeutic drug analysis, with a single system configuration. It means that methods can alternate easily with no need for human intervention, enabling smooth use in the clinical research laboratory.

2. Materials and Methods

The evaluated analytical system was a fully automated platform, from Shimadzu Corporation, composed of CLAM-2030 automation module, coupled to Nexera(TM)X2 UHPLC and LCMS-8060NX(TM) LC/MS/MS. HL-7 interface standards were used for bidirectional communication between the laboratory information system (LIS) (Dedalus, Germany) and the CLAM-LC/MS/MS. The target applications were Antibiotics, Direct Oral Anticoagulants, Antiepileptics, Neuroleptics, Antidepressant drugs (SSRI), Tricyclic Antidepressants, and Benzodiazepines. For each class of compounds, one individual method was developed, optimized, and validated (7 methods). All methods use similar analytical conditions, so that there is no need for system equilibration between two different methods. The fitness for purpose of this platform and these methods for 24/7 use was then evaluated by repeatedly requesting measurements for all methods in a random alternance.

3. Results

All validations results were within the acceptance criteria. Individual methods validations include isobars resolution (resolution above 1), calibration accuracy (QC and calibrant accuracy within 85-115%), LCMS repeatability (area, area ratio and ion ratio RSD below 10%), CLAM-LC/MS/MS method repeatability (area, area ratio and ion ratio RSD below 15%), day to day intermediate precision (area, area ratio and ion ratio RSD below 15%), mobile phase stability (retention time deviation below 2% after 2 weeks), LLOQ confirmation (signal-to-noise ratio above 10 and area RSD below 15%), matrix effect evaluation (matrix factor within 50-120%), absence of carryover confirmation (blank to LLOQ area ratio below 30%) and ring trial analysis (sample concentration accuracy within 85-115%). Also, repeated measurements for all methods in random alternance showed results within the acceptance criteria (QC, calibrant and sample accuracy within 85-115% and area, area ratio and ion ratio RSD below 15%).

4. Conclusion

This strategy proved its fitness for purpose for therapeutic drug analysis by LCMS for research projects. The fast LCMS methods which can alternate smoothly, and the automated sample extraction enable robust therapeutic drug analysis with a high throughput and at low cost, without compromising the user comfort.

Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19

Ryo Tamura[1], Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19 Kei Irie[2,5], Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19 Atsushi Nakagawa[3], Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19 Hirohito Muroi[1], Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19 Masaaki Eto[4], Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19 Hiroaki Ikesue[1], Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19 Nobuyuki Muroi[1,5], Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19 Shoji Fukushima[2], Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19 Keisuke Tomii[3], Population pharmacokinetics and exposure-clinical outcome relationship of remdesivir major metabolite GS-441524 in patients with moderate and severe COVID-19 Tohru Hashida[2,5]

[1]Department of Pharmacy, Kobe City Medical Center General Hospital, Kobe, Japan, [2]Faculty of Pharmaceutical Science, Kobe Gakuin University, Kobe, Japan, [3]Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan, [4]Department of Clinical Laboratory, Kobe City Medical Center General Hospital, Kobe, Japan, [5]Department of Clinical Pharmacy Research, Center for Clinical Research and Innovation, Kobe City Medical Center General Hospital, Kobe, Japan

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction:
Although remdesivir, a prodrug of nucleoside analog (GS-441524), has demonstrated clinical benefits in coronavirus disease 2019 (COVID-19) treatment, its pharmacokinetics (PKs) in patients with COVID-19 remain poorly understood. Therefore, in this study, the PKs of remdesivir and its major metabolite, GS-441524, were evaluated using a population PK (PopPK) approach to understand the PK aspect and exposure–clinical outcome relationship.

Materials and Methods:
The serum concentrations of remdesivir and GS-441524 (102 points in 39 patients) were measured using liquid chromatography–tandem mass spectrometry. All patients received 200 mg remdesivir on the first day, followed by 100 mg on 2–5 days, except for one patient who discontinued remdesivir on day 4. The median (range) age, body surface area, and estimated glomerular filtration rate (eGFR) were 70 (42–85), 1.74 m² (1.36–2.03), and 68 mL/min/1.73 m² (33–113), respectively. A compartment model with first-order elimination combined with remdesivir and GS-441524 was used for nonlinear mixed-effects model analysis.

Results:
Remdesivir was rapidly eliminated after infusion, whereas GS-441524 was eliminated relatively slowly (half-time = 17.1 h). The estimated apparent clearance (CL) and distribution volume of GS-441524 were 11.0 L/h (intersubject variability [ISV]% = 43.0%) and 271 L (ISV% = 58.1%), respectively. The CL of GS-441524 was significantly related to the eGFR ($CL \times [eGFR/68]^{0.745}$). The post hoc area under the curve of GS-441524 was unrelated to the recovery rate or aspartate aminotransferase/alanine aminotransferase elevation.

Discussions and Conclusions:
Overall, PopPK analysis showed the rapid elimination of remdesivir in the blood, and GS-441524 accumulation depended on eGFR in patients with COVID-19. However, no relevance of exposure–clinical outcome was not suggestive of the dose adjustment of remdesivir.

Capillary application of (volumetric) dried blood spot assays for tacrolimus and creatinine determination in stem cell transplant patients.

Pharmd Hanna De Baets[1]
[1]Ghent University, Ghent, Belgium

Immunosuppression 1, Sal D, september 25, 2023, 13:00 - 14:30

Introduction: Tacrolimus is the most commonly prescribed immunosuppressant drug in solid organ transplant recipients, and is also used in the field of allogeneic stem cell transplantation (alloSCT). To prevent Graft Failure and Graft-versus-Host Disease (GvHD), treatment with tacrolimus is an important component of the patients' therapy. Since tacrolimus is known to have a high inter- and intra-patient variability in addition to a narrow therapeutic window, follow-up of trough levels via therapeutic drug monitoring (TDM) is an absolute necessity to avoid over- and underexposure. Traditionally, tacrolimus concentrations are determined after a venous blood draw in the hospital. By adopting Dried Blood Spot (DBS) sampling following a finger prick, instead of conventional venous blood draws, this follow-up can (partially) be established from the patients' homes and has the potential to increase the patients' quality of life.
Material and methods: The aim of this study, which is still ongoing, is to evaluate the clinical applicability of capillary finger prick sampling for tacrolimus TDM and creatinine determination in the hospital (part 1), and in a home-sampling context (part 2), using conventional DBS subjected to fully automated extraction, and using Capitainer® qDBS devices, which are manually extracted. Previously, different liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis methods have been fully validated and the applicability on venous patient samples has been demonstrated. Additionally, sample quality and patients' experience will be assessed.
Results: For the first part of the study, venous (v-) and capillary (c-) DBS and qDBS, and whole blood (WB) were collected from alloSCT patients. Comparison of v-/c-DBS with WB (from 15 patients) and v-/c-qDBS with WB/plasma (from 24 patients) revealed a good agreement between all matrices for tacrolimus and creatinine. Both analytes met the pre-set clinical acceptance criterion that ≥80% of the samples should not differ more than 20% from the reference concentration in respectively whole blood and serum/plasma. Fifteen out of twenty-four patients agreed to also enroll for the second part of the study, using Capitainer® qDBS devices. This allowed longitudinal monitoring of the patients over time. Analysis of replicates revealed that the coefficient of variation (CV) (%) from sampling to analysis remained below 12 %. Additionally, patients who performed home-sampling made a quite positive assessment on the user-friendliness of Capitainer® qDBS-based microsampling.
Conclusion: Our results suggest that both capillary DBS and qDBS show great potential to be used as a complement to venous blood draws for TDM of tacrolimus and the determination of creatinine in alloSCT patients. However, an increased sample size is needed to further conclusively support these statements.

Pharmacokinetic variability and markers of toxicity of valproate in patients with refractory epilepsy

Martha Wolden[2], Johan Sætre[2], Katrine Heger[2], MD, PhD Erik Sætre[4], MD, PhD Margrete L Burns[3], MSc Signe F Kjeldsen[3], PhD Svein I Johannessen[3,4], Professor Cecilie Johannessen Landmark[1]
[1]Oslo Metropolitan University And National Center For Epilepsy And Dept Of Pharmacology, Oslo University Hospital, Oslo, Norway, [2]Oslo Metropolitan Unversity, Dept of Pharmacy, Oslo, Norway, [3]Section for Clinical Pharmacology, Dept of Pharmacology, Oslo University Hospital, Oslo, Norway, [4]National center for epilepsy, Oslo University hospital, Oslo, Norway

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction: Treatment with valproic acid (VPA) is associated with risk of liver toxicity,giving rise to hyperammonemia and elevation of liver enzymes. This may in severe cases lead to encefalopathy, coma and death. In addition, VPA has numerous pharmacokinetic challenges. This study aimed to investigate pharmacokinetic variability of total and unbound serum concentration measurements of VPA by therapeutic drug monitoring (TDM), and the role of biochemical analyses of ammonia and/or liver enzymes as markers of toxicity.
Materials and Method: Routine TDM-data from 2018-2022 including total and free serum concentrations of VPA, measurements of concomitantly used antiseizure medications (ASMs), and biochemical analyses of ammonia and liver enzymes. The study was approved by the Regional Ethics Committee.
Results: 704 measurements from 288 patients were included; 131 (45%)/157 (55%) women/men and mean age 28 (range 0-74). Mean VPA dose was 1183mg/day (150-3900), total VPA concentration 428 µmol/L (57-866), and unbound concentration 50 µmol/L (15-125). Mean ammonium concentration was 56 µmol/L (17-143). Extensive pharmacokinetic variability was observed; intraindividual variability in C/D-ratio was up to 25-fold, and 6-fold variability between the highest and lowest ammonium measurement. Ammonium levels above 85 µmol/L were associated with clinical signs of toxicity. There was a weak, statistically significant linear relationship between serum ammonia and total serum concentration of VPA ($R2=0.0141$)($p<0.05$). Mean serum alanine aminotransferase (ALAT) concentration was 27 U/L (7-551). There was no linear relationship between total VPA concentration and ALAT level.
Discussions and Conclusions: This study revealed extensive pharmacokinetic variability of VPA. We suggest that combined measurements of total and unbound VPA serum concentrations with analyses of ammonium and liver enzymes may serve as tailored monitoring to aid clinical decision-making in patients with refractory epilepsy and symptoms of toxicity.

Near-infrared-based hematocrit prediction using volumetric absorptive microsampling devices: an in-depth evaluation

Laura Boffel[1], Pharm. D. Liesl Heughebaert[1], Dr. Stijn Lambrecht[2], Dr. Christoph Lühr[3], Prof. Dr. Christophe Stove[1]
[1]Ghent University, Ghent, Belgium, [2]Ghent University Hospital, Ghent, Belgium, [3]BÜCHI Labortechnik GmbH, Essen, Germany

Alternative sampling strategies 2, Møterom 1, september 26, 2023, 13:00 - 14:30

INTRODUCTION: Volumetric absorptive microsampling (VAMS), where a fixed volume of blood, independent of the hematocrit (Hct), is wicked up by the absorbent tip of the collection device, has been suggested as an alternative to dried blood spot (DBS) sampling. By using a volumetric blood sampling device, the Hct-based area bias related to partial-punch DBS analysis is circumvented. Nevertheless, a Hct-based recovery and matrix effect bias can still affect the accuracy of the VAMS-based blood results. Moreover, reference values or intervals are typically established in plasma or serum. Hence, knowledge of the Hct is required when aiming at converting VAMS-based results to plasma or serum results to allow comparison, since an analyte's blood to plasma ratio may be Hct-dependent. Although highly relevant, only a limited number of strategies to predict the Hct from a VAMS sample are available. Here, we evaluated near-infrared (NIR)-based spectroscopy, which has already been shown to allow Hct prediction from non-volumetrically applied DBS, as a novel technology for the Hct prediction of VAMS.
MATERIALS AND METHODS: A fit-for-purpose custom-made NIR set-up was used for the Hct predictions. Using left-over EDTA-anticoagulated patient samples, a calibration model based on 10 µL VAMS samples was set up (n = 90) (Hct range: 0.157 to 0.540 L/L). Calibration samples were measured after storage at room temperature (up to one month) and at 60 °C, to evaluate whether storage of the samples had an influence on the Hct prediction in an early stage. Prior to validation of the method, the performance of the calibration model was evaluated using data obtained from an independent set of venous patient samples (n = 24). In-depth validation of the method, including evaluation of accuracy and inter- and intra-day precision, is being performed using an independent set of quality control (QC) patient samples (n = 48). Also, the influence on the Hct prediction of different storage conditions, multiple clinical parameters and VAMS-related variables, including over- and underfilling of the VAMS tip and different VAMS sample volumes (20 µL and 30 µL), will be evaluated using a subset of the QC samples (n = 24).
RESULTS: Based on the available data from an independent set of venous patient samples, the accuracy and inter-day precision were calculated. Overall, while the calibration model is still being improved, promising results were already obtained for samples with a Hct < 0.50 L/L, with the bias and inter-day precision ranging from -0.037 to 0.021 L/L and from 4.91 to 9.05 %, respectively.
CONCLUSION: Overall, although with the current calibration model the bias obtained for samples with a Hct > 0.50 L/L was still higher than the pre-set acceptance limit of +/- 0.050 L/L, promising results were obtained for VAMS samples with lower Hct values. Further refining the calibration model is expected to further improve the Hct predictions – also for higher Hct values.

Modelling changes in the pharmacokinetics of tacrolimus during pregnancy after kidney transplantation: a retrospective cohort study

Drs. Maaike Schagen[1,2], PharmD Asiye Nur Ulu[2], Bsc Marith Francke[1,2], Prof. dr. Ron van Schaik[3], Dr. Jacqueline van de Wetering[1], Dr. Marleen van Buren[1], Dr. Dennis Hesselink[1], PharmD, PhD Brenda de Winter[2]

[1]Erasmus Medical Center Transplant Institute, Department of Internal Medicine, University Medical Center Rotterdam, Rotterdam, Netherlands, [2]Rotterdam Clinical Pharmacometrics Group, Department of Hospital Pharmacy, University Medical Center Rotterdam, Rotterdam, Netherlands, [3]Department of Clinical Chemistry, University Medical Center Rotterdam, , Rotterdam, Netherlands

Pharmacometrics, Møterom 5, september 25, 2023, 13:00 - 14:30

Introduction: Pregnancy after kidney transplantation is a realistic option but immunosuppressants must be continued during gestation. However, maintaining tacrolimus whole-blood pre-dose concentrations is complicated as physiological changes during pregnancy affect the pharmacokinetics of and hence exposure to tacrolimus. The aim of this study was to investigate the changes in tacrolimus whole-blood pre-dose concentrations throughout pregnancy in kidney transplant recipients and correlate these with covariates in a population pharmacokinetic (popPK) model.
Materials and Methods: Data of pregnant women using a twice-daily oral tacrolimus formulation after kidney transplantation were retrospectively collected from six months before conception, throughout gestation, and up to six months postpartum. This included data on tacrolimus exposure, and demographic, clinical and genetic parameters. Pharmacokinetic analysis was performed using non-linear mixed effects modelling software (NONMEM). The final model was evaluated using goodness-of-fit plots, visual predictive checks, and a bootstrap analysis. Finally, a simulation trial was performed for the different stages of follow-up (pre-pregnancy, the trimesters, post-partum).
Results: Fourteen women using the twice-daily oral tacrolimus formulation and who had a successful pregnancy after a kidney transplantation were included. A total of 260 whole-blood tacrolimus pre-dose concentrations were available. Tacrolimus concentrations ranged from 1.4 to 14 ng/mL, tacrolimus doses ranged from 2 to 22 mg/day. Tacrolimus apparent clearance (CL/F) increased during pregnancy from 33.2 to 41.9 L/h, with the highest change observed in the first trimester. Haematocrit (delta objective function value (ΔOFV) -86.46) and gestational age (ΔOFV = -57.39) were negatively correlated with CL/F (p-value <0.01). These covariates explained 45% of the inter-individual and 82% of the inter-occasion variability on CL/F. Simulated whole-blood tacrolimus pre-dose concentrations, with the gestational age correlated to mean haematocrit values of that period, show a clear distinction between non-pregnant state and pregnancy on CL/F. A rapid decrease in tacrolimus concentrations occurred during the first trimester, which decreased a bit further during the second trimester and stayed stable during the last trimester. This change rapidly disappeared postpartum.
Discussions and Conclusions: Gestational age and haematocrit impact the exposure to tacrolimus during pregnancy. To maintain target whole-blood tacrolimus pre-dose concentrations during pregnancy, a dose increase is suggested. This popPK model may be used in the future for tacrolimus dose adjustments in pregnant kidney transplant recipients.

Significance of CYP3A5 Polymorphism Analysis in the Prophylaxis of Graft-versus-Host Disease with Tacrolimus

Dr. Naoki Yoshikawa[1], Prof. Ryuji Ikeda[1]
[1]Department of Pharmacy, University of Miyazaki Hospital, Miyazaki, Japan

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction: Hematopoietic stem cell transplantation (HSCT) is used to treat blood and hematopoietic tissue abnormalities. Although HSCT is effective, some patients develop graft-versus-host disease (GVHD) after allogeneic HSCT. Tacrolimus is a key prophylactic drug against GVHD. The pharmacokinetics of tacrolimus vary significantly among individuals. Therefore, therapeutic drug monitoring is required when using tacrolimus. Polymorphisms in the gene encoding cytochrome P450 (CYP) 3A5 particularly influence the pharmacokinetics of tacrolimus in Japanese patients. In the present study, the relationship between individual differences in tacrolimus blood concentration changes and CYP3A5 polymorphisms was analyzed in HSCT recipients, focusing on the period of increased blood concentration of the drug at the start of administration, during which drug metabolism strongly contributes to drug accumulation.
Materials and Methods: The patients in this study underwent their first allogeneic HSCT between January 2018 and October 2020 and were administered tacrolimus for GVHD prophylaxis through continuous infusion. This was a prospective, observational cohort study. After obtaining consent, blood collected from the subjects before pre-transplant conditioning was used for CYP3A5 polymorphism analysis. A quenching probe method was used to genotype the CYP3A5 6986A>G (*3) allele. The day following the start of tacrolimus administration was set as day 1, and the whole-blood tacrolimus concentration was measured on days 1–5. The tacrolimus blood concentration on days 1–5 was divided by the dose per body weight to calculate the concentration/dose (C/D) ratio.
Results: Nine patients were assigned to the *1/*3 group and 11 patients were assigned to the *3/*3 group. None of the participants were homozygous for the *1 allele. The C/D ratio increased from day 1 and was largely stable by day 5. A significant difference was observed between the *1/*3 and *3/*3 groups in the time course of the C/D ratio during this period (repeated measures ANOVA, $p = 0.045$). After day 3, the C/D ratio in the *3/*3 group was significantly higher than that in the *1/*3 group on all days. The frequency of acute GVHD during the observation period was higher in the *1/*3 group than in the *3/*3 group ($p = 0.049$). In addition, there was a significant difference in the cumulative incidence of acute GVHD between the two groups ($p = 0.019$). Blood tacrolimus concentrations were maintained at approximately the target concentrations when GVHD was observed.
Discussions and Conclusions: In this study, we clarified the relationship between individual differences in tacrolimus blood concentration changes and CYP3A5 polymorphisms after starting continuous infusion in allogeneic HSCT recipients. The pharmacokinetics of tacrolimus are affected by a variety of factors, particularly its absorption and metabolism. However, as the pharmacokinetics of continuous infusion were analyzed, the potential influence of the absorption process was considered negligible. Therefore, CYP3A5 polymorphism, e.g., individual differences in drug metabolism, is an important factor that determines the changes in tacrolimus blood concentration at the start of administration. In addition, we demonstrated that the *3 polymorphism in the gene encoding the drug-metabolizing enzyme CYP3A5 is associated with acute GVHD development after allogeneic HSCT, independent of tacrolimus levels in the blood.

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Adalimumab through levels as a predictor of patient-reported outcomes and disease activity in rheumatoid arthritis

PharmD Juul Cox[1,2,3], Dr. PharmD Tessa Bosch[1,2], Prof. dr. Angelique Weel[3,4]
[1]Hospital Pharmacy, Maasstad Hospital, Rotterdam, Netherlands, [2]Clinical Pharmacology and Toxicology, MaasstadLab Maasstad Hospital, Rotterdam, Netherlands, [3]Erasmus School of Health Policy & Management, Erasmus University Rotterdam, Rotterdam, Netherlands, [4]Rheumatology, Maasstad Hospital, Rotterdam, Netherlands

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction: Pharmacotherapy with biological Disease-Modifying Anti Rheumatic Drugs (bDMARDs) for patients with rheumatoid arthritis (RA) was originally introduced in a one-size-fits-all dosage. However, a significant proportion of patients appear to be either over- or under-treated, ultimately leading to a loss in quality of life. Studies suggest a relationship between serum trough levels and response to therapy, but evidence on the effect is limited. Moreover, patient-reported outcome measures (PROMs) are used more and more to provide relevant information about the impact of the disease from a patient perspective. Currently, there is no information about the effect of biological serum levels on PROMs. Therefore, this study aims to assess the correlation of serum trough levels of adalimumab in RA patients with scores on DAS, HAQ-DI, FACIT-F, RAID, and EQ-5D.

Materials and Methods: We aim to include adalimumab-treated RA patients who are TDM-naïve initially and have available data on PROMs before and after TDM of adalimumab. Trough levels and Patient-reported Outcomes (PROs) under the same dose regimen are linked. Serum trough samples of adalimumab are drawn within 4 days before a next dose of adalimumab. A hospital pharmacist evaluates the drug levels and categorizes them. Trough levels of adalimumab are tested for association with DAS and PROMs. The statistical analysis will be conducted using StataSE 14 for Windows.

Results: Our study aims to explore the correlation between serum trough levels of adalimumab and patient-reported outcomes in rheumatoid arthritis (RA) patients. Currently we have enrolled 79 patients. Preliminary results indicate that 25 patients have levels within the therapeutic range (5-8 mg/L), while 23 have levels above 8 mg/L and 30 have levels below 5 mg/L. Among the 30 patients with low levels, 4 had non-detectable adalimumab serum through levels at the time of measurement. Moreover, 10 patients had detectable adalimumab antibodies and 20 did not. Only 4 patients had drug antibodies exceeding 30 U/mL, with 2 exceeding 980 U/mL. Further analysis will provide additional insights into these findings, including the assessment of and correlation with PROs and the Disease Activity Score (DAS), and subgroup analyses will also be conducted.

Conclusion: If drug levels correspond to outcomes that matter to patients, therapeutic drug monitoring is of added value, ultimately leading to fully personalized and cost-effective healthcare management of RA patients. This study aims to provide additional evidence on the effect of TDM on PROMs.

Implementation of finger prick blood sampling to support TDM of biologics: biologics concentration combined with an inflammatory marker

Phd Maurice Steenhuis[1], PhD Annick de Vries[1], PhD Theo Rispens[6], Tim Otten[2], Marijn Visschedijk[2], Arno Bourgonje, Alyssa Toorop[3], Zoé van Kempen, Laura Boekel, Yaëlle Besten[4], Joep Killestein[3], Gertjan Wolbink[4], Sander Tas[5], PhD Floris Loeff[1], Annick de Vries[1]
[1]Sanquin Diagnostic Services, Amsterdam, Netherlands, [2]Department of Gastroenterology, University Medical Centre Groningen, Groningen, The Netherlands, , , [3]Neurology Outpatient Clinic, Amsterdam UMC location Vrije Universiteit Amsterdam, Amsterdam, The Netherlands., , , [4]Amsterdam Rheumatology and Immunology Center, location Reade, Department of Rheumatology, Amsterdam, Netherlands., , , [5]Department of Rheumatology and Clinical, Amsterdam UMC, location AMC, University of Amsterdam, Amsterdam, the Netherlands., , , [6]Department of immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, Amsterdam, the Netherlands., ,
Alternative sampling strategies 2, Møterom 1, september 26, 2023, 13:00 - 14:30

Introduction
We have successfully developed and implemented the use of finger prick blood sampling at-home for therapeutic drug monitoring (TDM) of biologics. Travel restrictions during the COVID-19 pandemic increased platform for home-sampling. As we had the method up-and-running this was fuelled by measuring SARS-CoV-2 antibody levels; we screened almost 100.000 participants.
To support the clinic we combined measuring the concentration of biotherapeutics and an inflammatory marker. Here we report on the use of finger pricks to measure concentration of the monoclonal anti-inflammatory drugs natalizumab, infliximab and vedolizumab, and the infection biomarker C-reactive protein (CRP) in capillary blood samples, collected by the patient at home. In addition, we have evaluated the success rate and patients' perspective towards to use of the finger prick blood sampling at home.

Materials and Methods
Capillary blood samples by finger prick and intravenous blood samples were collected to assess drug concentrations prior to intravenous administration of the biologics natalizumab (n=30), infliximab (n=46) and vedolizumab (n=35). The finger prick was either performed by a healthcare professional or by the patient and sent by postal service to us for analysis. Serum concentration of the biologics and CRP (n=81) were analysed with an enzyme-linked immunosorbent assay and results were compared using Blant-Altman, Spearman correlation or Cohen's kappa.

Results
Serum natalizumab concentrations measured in capillary and intravenous blood samples correlated well ($r = 0.96$, $p < 0.001$) and both methods showed a high degree of agreement with a mean bias of -0.36 ug/mL. Similar data was found for infliximab and vedolizumab with a mean bias of 0.42 ug/ml and 0.72 ug/ml, respectively. Venous and capillary CRP concentrations correlated well ($r = 0.99$, $P < 0.001$). When CRP concentrations were categorised as low (<5 mg/L) and clinically elevated (>5 mg/L), Cohen's kappa was 0.91 (95% CI: 0.84-0.98, P<0.001), demonstrating excellent agreement. Most patients (>95%) were able to successfully perform the self-sampling at home without prior instructions and the majority of patients were willing to perform self-sampling periodically in the future.

Discussion and Conclusion
These studies show that finger prick home sampling is suitable for a high-throughput implementation to monitor patients remotely, which will contribute to improving the efficiency and cost-effectiveness of both healthcare and scientific research. Most importantly, home monitoring can improve the patient's quality of life and patients are not dependent anymore on hospital visits. Physicians can safely and timely monitor biologic drug concentrations and CRP by a finger prick to

implement TDM. Most patients participating experienced the self-sampling as a straightforward and feasible test, reflecting a high degree of patient support, tolerability, and practicality. Taken together, finger prick blood collection would enable physicians to monitor patients at home without additional intravenous blood draws and without patient travelling to a healthcare facility, which is cost-effective and can support personalised dosing.

Pharmacokinetic variability of cannabidiol and its metabolites in patients with refractory epilepsy

Johan Sætre[2], Martha Wolden[2], PhD André Gottås[3], MSc Tao McQuade[4], MSc Signe F Kjeldsen[3], MD Anne Våtevik[5], MD, PhD Erik Sætre[5], MD, PhD Torleiv Svendsen[5,6], MD, PhD Margrete L Burns[3], PhD Svein I Johannessen[3,5], PhD Elisabeth L Øiestad[4], Professor Cecilie Johannessen Landmark[1]
[1]Oslo Metropolitan University and National Center For Epilepsy And Dept Of Pharmacology, Oslo University Hospital, , Norway, [2]Oslo Metropolitan University, Dept of Pharmacy, Oslo, Norway, [3]Section for clinical pharmacology, Dept of pharmacology, Oslo university hospital, Oslo, Norway, [4]Dept of Forensic Medicine, Oslo University Hospital, Oslo, Norway, [5]National Center for Epilepsy, Oslo University hospital, Oslo, Norway, [6]Lillehammer Hospital trust, Lillehammer, Norway

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction: Cannabidiol (CBD) (Epidyolex) is a new antiseizure medication (ASM) used in rare and severe epileptic syndromes. CBD has numerous pharmacokinetic challenges, including low and variable absorption, high protein binding, and enzyme inhibition. The purpose was to investigate pharmacokinetic variability of CBD and its metabolites to elucidate relationships between doses and measured serum concentrations.
Materials and methods: Data on serum concentrations of all ASMs, CBD and metabolites 7-OH-CBD (pharmacologically active) and 7-COOH-CBD were collected during 08.2022-04.2023. Serum concentration measurements were performed at Section for Clinical Pharmacology, National Center for Epilepsy, and Dept of Forensic Medicine, Oslo University Hospital. The study was approved by the Regional Ethics Committee.
Results: Data from 52 patients were included, 164 serum concentration measurements (1-8 per patient). Mean age was 23 (range 3-55) years. Mean CBD dose was 427 mg/day (range 100-1200 mg/day), mean CBD serum concentration 0.23 □mol/L (range 0,011-2,56 □mol/L) (reference range 0.15-0.45 □mol/L), 7-OH-CBD 0.101 □mol/L (range 0-0.69 □mol/L) and 7-COOH-CBD 7,18 □mol/L (range 0,2-44,51 □mol/L). The interindividual pharmacokinetic variability was extensive; 11-fold variation in concentration/dose-ratio of CBD (0.0001-0.0012 □mol/L/mg), and 25-fold in concentration-ratio of 7-OH-CBD/CBD (0.06-0.46 □mol/L). Intraindividual variability in C/D-ratio was up to 3-fold. Linear regression demonstrated moderate, statistically significant linear correlation between dose and concentration ($r^2=0.28$)($p<0.05$). Twenty different ASMs were used in combination with CBD, most commonly clobazam (n=43) and valproate (n=26), and 10 patients used stiripentol. Concentration ratios of clobazam/desmethyl-clobazam increased significantly by 68% (11.6-19.5) ($p<0.05$) from start to maintenance treatment, pointing to CBD-mediated inhibition of CYP2C19.
Discussion and Conclusions: This TDM-study revealed extensive interindividual pharmacokinetic variability of CBD and the 7-OH-metabolite relevant to measure in patients with severe and refractory epilepsy. The present results demonstrate a need for close follow-up and use of TDM to give an optimal and individualized treatment with CBD.

Extensive pharmacokinetic variability of topiramate in women of childbearing age

Aleksandra Janiga[2], MD, PhD Margrete L Burns[3], MSc Pharm Katrine Heger[2], PhD Svein I Johannessen[3,4], Professor Cecilie Johannessen Landmark[1]
[1]Oslo Metropolitan University And National Center For Epilepsy And Dept Of Pharmacology, Oslo University Hospital, , Norway, [2]Oslo Metropolitan University, Dept of Pharmacy, Oslo, Norway, [3]Section for Clinical Pharmacology, Dept of Pharmacology, Oslo University Hospital, Oslo, Norway, [4]National Center for Epilepsy, Oslo University Hospital, Oslo, Norway

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction: Topiramate is an antiseizure medication which is increasingly used in women with epilepsy, often as an alternative to valproic acid. Recent studies demonstrate an increased risk of neurocognitive developmental effects in the offspring also of topiramate, with doses from 100 mg/day. The purpose was to investigate pharmacokinetic variability of topiramate in women with epilepsy of childbearing age to elucidate the unpredictable relationship between the dosages used and the exposure in the body in the individual woman and consequently in the fetus.
Material and Methods: Retrospective quantitative data from the therapeutic drug monitoring (TDM) database at the Section for Clinical Pharmacology, the National Center for Epilepsy, Norway, were used. Data were collected from women of childbearing age, 14-46 years, who were treated with topiramate during 2020-22.
Results: TDM data from 230 female patients were included, 629 serum concentration measurements (1-17 per patient). Mean age was 31 years and weight 72 kg (listed in 32%). Mean dose was 238 mg/day (median 200 mg), and mean serum concentration 20 µmol/L (median 18) (reference range 6-30 µmol/L). Only 37 measurements (from 23 patients) had doses of <100 mg/day (6%). The interindividual pharmacokinetic variability was extensive, as illustrated by a 13-fold variability in concentration/dose ratios (0.022 to 0.28 µmol/L/mg). The most common dose of 200 mg/day showed serum concentrations in the range of 5-35 µmol/L. Linear regression demonstrated moderate, statistically significant linear correlation between dose and concentration ($r^2=0.50$)($p<<0.001$). The most common comedications were lamotrigine (n=65), levetiracetam (n=52), and valproate (n=45).
Discussion and Conclusions: This TDM-study of topiramate revealed extensive interindividual pharmacokinetic variability of topiramate in women of childbearing age. The present results call for close follow-up, including the use of TDM to aid decision-making and reduce potential harmful effects.

Establishment of a quantification method for tegafur, 5-fluorouracil, and gimeracil in human plasma obtained from older adults treated with S-1

Dr. Motozumi Ando[1], Ms. Riko Seike[1], Ms. Saori Gocho[2], Ms. Shoko Maeda[2], Associate professor Norio Watanabe[1], Dr. Masami Inagaki[2], Professor Masami Kawahara[1]
[1]Department of Clinical Pharmacy and Sciences, School of Pharmacy, Aichi Gakuin University, Nagoya, Japan, [2]Department of Pharmacy, Nagoya Ekisaikai Hospital, Nagoya, Japan

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction

S-1 is a major oral anticancer agent primarily used for the treatment of gastric cancer and consists of a combination of tegafur, gimeracil, and potassium oxonate. After administration, tegafur is metabolized to the active metabolite 5-fluorouracil (5-FU). Gimeracil impedes the degradation of 5-FU by inhibiting the activity of dihydropyrimidine dehydrogenase. Recently, there has been an increase in the use of S-1 among older patients with cancer. However, there are concerns that age-related renal dysfunction may reduce gimeracil excretion and increase 5-FU concentration in the blood. Nevertheless, there is limited clinical information on this matter. The aim of this study was to establish a quantification method for gimeracil, tegafur, and 5-FU in human plasma using liquid chromatography equipped with tandem mass spectrometry (LC-MS/MS). Subsequently, this method was used to measure these compounds in plasma samples obtained from older adults who had received S-1 treatment.

Methods

To analyze tegafur and 5-FU, 5-chlorouracil (5-CU) was used as the internal standard. The following transitions were used in the LC-MS/MS analysis: m/z 186.85 → 128.0 (+) for gimeracil, 198.90 → 42.10 (-) for tegafur, 128.95 → 42.05 (-) for 5-FU, and 145.05 → 42.05 (-) for 5-CU. Tegafur and 5-FU were extracted from plasma using liquid-liquid extraction column; and gimeracil was extracted using a spin-type extraction column for hydrophilic compounds. A total of 12 samples were collected from three patients with cancer who were >65 years of age and received S-1 treatment. Among the 12 samples, six were collected near the trough point and the others were done during 2 h after administration.

Results

The LC-MS/MS analysis method provided rapid confirmation of all analytes and the internal standard, with a total run time of 4 min. The calibration curve was linear over the concentration ranges of 5–500 ng/mL, 10–5000 ng/mL, and 2–1000 ng/mL for gimeracil, tegafur, and 5-FU, respectively. This method provided accuracy within 19.3% and precision below 12.8% for all three analytes. Using this approach, the concentration of gimeracil, tegafur, and 5-FU were measured in the patients' plasma samples. The concentration ranges observed were 31.1–252.9 ng/mL, 694.2–4766.1 ng/mL, and 12.9–439.1 ng/mL for gimeracil, tegafur, and 5-FU, respectively.

Discussion and Conclusions

We have successfully developed a reliable method for measuring gimeracil, tegafur, and 5-FU in human plasma using LC-MS/MS. The concentrations of these analytes in plasma samples obtained from three patients with cancer were found to be within the range of their respective calibration curve. Therefore, this method could be utilized to determine plasma levels of gimeracil, tegafur, and 5-FU in clinical settings. Subsequently, we intend to use this method for assessing the blood concentration and pharmacokinetics of gimeracil, tegafur, and 5-FU, specifically in older patients with cancer.

How sure you can be of the results of quantification of psychoactive compounds in blood?

MSc Anna Lenartowicz[1], PhD Julia Mironenka[1], PhD Rafał Szewczyk[1,2], PhD Adrian Soboń[1,2], PhD Katarzyna Krupczyńska-Stopa[1,2], PhD Maciej Stopa[1,2], MSc Andrzej Kwaśnica[3]
[1]LabExperts sp. z o. o., Gdańsk, Poland, [2]Bioanalytic sp. z o. o., Gdańsk, Poland, [3]Lab4Tox sp. z o. o., Wrocław, Poland

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

1. Introduction

Compound presence confirmation is one of the key aspects of targeted and quantitative analysis in forensics applications. High resolution tandem mass spectrometry (HR-MS/MS) may become a major tool for this kind of analysis because of its mass accuracy resulting in unparallel specificity, all combined with broad linearity and scanning speed achieved in the newest hardware on the market. In this work we show a modern HR-MS/MS method for sensitive detection of 27 analytes with high confidence in venous blood and capillary blood collected on a volumetric absorptive microsampling (VAMS) probe. Analytes include: Tramadol, Morphine, Fentanyl, Methadone, Codeine, Alprazolam, Diazepam, Flunitrazepam, Lorazepam, Oxazepam, Zopiclone, Clonazepam, Nordiazepam, Zolpidem, Hydroxyzine, Amphetamine, Methamphetamine, MDA, MDMA, MDEA, THC, Cocaine, 6-acetylmorphine, 7-aminoflunitrazepam, 7-aminoclonazepam, Benzoylecgonine, THC-COOH.

2. Materials and Methods

Briefly, sample preparation included: spiking of internal standards, protein precipitation and extraction using acetonitrile:methanol (1:1) with 0.1% formic acid, evaporation under nitrogen stream and reconstitution in LC mobile phase. Compounds were analyzed using reversed-phase chromatography on ExionAC LC coupled with ZenoTOF 7600 (SCIEX) operating in positive electrospray ionization scheduled MRMhr mode acquiring full MS/MS spectra for each compound. Developed processing method use multi-level confirmation and combined scoring based on HR data where result is affected by 5 criteria that have different decision weights: MS/MS library confirmation (50%), precursor ion mass defect (20%), quantifier ion mass defect (20%), precursor ion isotope pattern (5%) and retention time (5%). Each criterium contributes in the combined score calculation and has its own range of 3-level acceptance in ppm, % or seconds, respectively. The cut-off point of combined score is estimated at 70% after series of analysis and allows flawless reporting of compounds from DRUID list. Data were processed in SCIEX OS software.

3. Results

The method was validated separately for venous blood and capillary blood collected on VAMS and fulfilled the following criteria for each analyte: linearity ($R \geq 0.995$), working range (LLOQ – 50 ng/ml), reproducibility (%CV ≤ 15%), accuracy (80 - 120%) and recovery (80 - 120%). For majority of analytes included in the method LLOQ was in the range 0.01- 0.05 ng/ml (ex. Diazepam, Codeine, Morphine, MDA) for venous blood and 0.05-0.1 ng/ml for VAMS sampler. For analytes such as Tramadol, Fentanyl, Methadone and Cocaine the LLOQ ranged between 0.001- 0.005 ng/ml for venous blood and 0.01-0.05 for VAMS. The method was successfully applied to routine analysis of blood samples.

4. Discussions and Conclusions

Quantitative LC-MS/MS method was validated according to the international recommendations. The greatest advantage of presented method is its high specificity and extremely low Limits of Quantitation. Most of described in literature LC-MS/MS methods used for psychoactive compounds quantification are based on MRM scanning mode with triple quadrupole instruments. Such approach does not allow to obtain sufficiently high specificity because of difficult data interpretation at low concentrations of analytes in real-life samples where MRM ratio and matrix interferences leads to data misinterpretation. Developed method allows sensitive, specific and false positive resistant HR-MS/MS quantitation of 27 psychoactive compounds in venous and capillary blood.

Automation of sample preparation for the quantification of tacrolimus and cyclosporine in volumetric absorptive microsamples

PhD Sofia Lindahl[1], B.Sc. Karin Pettersen[1], Professor Anders Åsberg[1,2], MD PhD Karsten Midtvedt[1,2], PhD Stein Bergan[1,2], PhD Nils Tore Vethe[1]
[1]Oslo University Hospital, Oslo, Norway, [2]University of Oslo, Oslo, Norway

Alternative Sampling Strategies 1, Møterom 1, september 25, 2023, 13:00 - 14:30

Introduction

Tacrolimus and cyclosporine are immunosuppressant drugs, commonly measured in blood for therapeutic drug monitoring (TDM). Volumetric absorptive microsampling (VAMS®) is an alternative to venous blood sampling. Application of self-collected VAMS for TDM are patient friendly but the manual sample preparation procedure is time-consuming in the lab. There are publications regarding the combination of VAMS® and TDM of immunosuppressants, but few where the sample preparation is performed on an automated liquid handler system.

Materials and Methods

The VAMS device used was the Mitra® 10 µL (Trajan Scientific and Medical, Melbourne, Australia). Patient samples were excess material from routine analysis of tacrolimus and cyclosporine (EDTA whole blood). For automated sample preparation, a Starlet liquid handler from Hamilton (Bonaduz, Switzerland) was used. The protocol applied for both manual and automated sample preparation was based on the method by Vethe et al., with the following adaptions: increased water volume from 100 µL to 125 µL for both setups and an extra shaking pre-step (5 minutes at 500 rpm) in the manual procedure. The samples were quantified using LC-MS/MS.

Results

The preliminary precision results (CV) for tacrolimus and cyclosporine using Mitra® (5 different concentrations levels; tacrolimus 0.7-26.4 µg/L, cyclosporine 10-646 µg/L) prepared manually or automated was 4.1-9.2% and 3.3-12.2% for tacrolimus, respectively, and 3.1-8.0% and 2.8-8.5% for cyclosporine, respectively.
The percent of samples within a ±20% deviation (P20) in measured concentration of tacrolimus and cyclosporine for Mitra® prepared automated versus manually was 100% for tacrolimus (n=30) and 96.7% for cyclosporine (n=30). P20 was also assessed for Mitra® samples compared to liquid EDTA whole blood, prepared manually or automated. For tacrolimus P20 was 96.7% (n=30) for both manually and automated preparation. For cyclosporine, P20 was 90.0 % and 96.7% (n=30) for manually and automated, respectively.
For method comparison Passing-Bablok regression analysis was also performed. The equations for tacrolimus were: y=-0.129+1.01x (automated Mitra vs manual Mitra), y=-0.00124+0.987x (automated Mitra vs liquid sample) and y=1.33e-15+1.00x (manual Mitra vs liquid sample). The equations for cyclosporine were: y=3.19 + 0.948x (automated Mitra vs manual Mitra), y=3.09+0.988x (automated Mitra vs liquid sample) and y=1.78+1.03x (manual Mitra vs liquid sample).

Discussions and Conclusions

Finger-prick sampling using VAMS is implemented for home-based self-collection of blood samples after transplantation. In the present study, we showed good agreement between tacrolimus and cyclosporine concentrations obtained by automated and manual preparation of Mitra® samples. There was also a good agreement with analyses performed in ordinary liquid blood. In the laboratory, automation of the Mitra® sample preparation will save manual labor and the risk of error will be minimized. The automated protocol is feasible for implementation.

Impact of Inflammation on Intra-individual Variation in Trough Voriconazole Concentration in Patients with Hematological Malignancies

Dr. Ryota Tanaka[1], Mrs. Yu Maeda[1], Mr. Ryosuke Tatsuta[1], Dr. Kuniko Takano[2], Dr. Takehiro Hashimoto[3], Prof. Masao Ogata[2], Prof. Kazufumi Hiramatsu[3], Prof. Hiroki Itoh[1]
[1]Department of Clinical Pharmacy, Oita University Hospital, Yufu, Japan, [2]Department of Hematology, Oita University Hospital, Yufu, Japan, [3]Hospital Infection Control Center, Oita University Hospital, Yufu, Japan

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Background: The pharmacokinetics of voriconazole (VRCZ) shows large intra-individual and inter-individual variability and is affected by various factors. Recently, inflammation has been focused on as a significant factor affecting the variability. This study aimed to compare the influence of C-reactive protein (CRP) and other clinical laboratory parameters on intra-individual variability in trough VRCZ concentration and examine the impact of inflammation in patients with hematological malignancies. Methods: We conducted a retrospective, single-center, observational cohort study. Medical records were reviewed to identify patients with hematological malignancy who received oral VRCZ for prophylaxis against deep mycosis and underwent multiple therapeutic drug monitoring between April 2010 and March 2020 at the Department of Hematology in Oita University Hospital. Quantitative changes in pharmacological and clinical laboratory parameters (Δ) were calculated as the difference between the current and preceding measurements. The study was initiated after approval by the Ethics Committee of Oita University Faculty of Medicine (Review reference number: 1990). Results: Using the measurements of 202 trough samples obtained from 42 patients who satisfied the selection criteria, we analyzed the correlation of VRCZ concentration/maintenance dose per weight (C/D) with each laboratory data. VRCZ C/D was found to correlate positively with CRP level ($n = 202$, $rs = 0.314$, $p < 0.001$). Furthermore, ΔC/D correlated positively with ΔCRP level ($n = 160$, $rs = 0.442$, $p < 0.001$), and ΔCRP showed the highest correlation coefficient among the laboratory parameters. Univariate and multivariate analyses identified ΔCRP ($p < 0.001$) and Δgamma-glutamyl transpeptidase (γGTP) ($p = 0.019$) as independent factors associated with ΔC/D. Partial R^2 were 0.315 for ΔCRP and 0.024 for ΔγGTP, suggesting markedly greater contribution of ΔCRP to ΔC/D. Conclusions: Changes in CRP and γGTP were identified to be independently associated with a change in C/D of VRCZ, and the contribution of ΔCRP was much greater than that of γGTP. Hematological malignancy patients have many factors that cause fluctuation in CRP levels, such as breakthrough febrile neutropenia, successful antibacterial treatment, and blood cell recovery. Since clinical laboratory parameters other than CRP had little influence on trough plasma VRCZ concentration, therapeutic drug monitoring and dose adjustment considering fluctuation in CRP level would be important for proper use of VRCZ in patients with hematological malignancies.

Effect of CYP2D6 Genotype on Duloxetine Serum Concentration

Dr Kristine Hole[1,2], Dr Tore Haslemo[1,2], Prof Espen Molden[1,3]
[1]Diakonhjemmet Hospital, Oslo, Norway, [2]Oslo Metropolitan University, Oslo, Norway, [3]University of Oslo, Oslo, Norway

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction: Duloxetine is a serotonin and norepinephrine reuptake inhibitor metabolized by CYP1A2 and CYP2D6. The existing data is scarce on the clinical impact of CYP2D6 genotype on duloxetine exposure. To elucidate this issue, the aim of the present study was to investigate the impact of CYP2D6 genotype on duloxetine serum concentration while adjusting for patient age and sex.

Material and methods: Patients were retrospectively included from a therapeutic drug monitoring database if they had measured duloxetine serum concentration and analyzed CYP2D6 genotype between 2010-2022. The impact of CYP2D6 genotype, age and sex on duloxetine concentration to dose (C/D) ratio was investigated by multiple linear regression analysis.

Results: In total, 315 patients were included in the study; 23 CYP2D6 poor metabolizers (PMs), 141 intermediate metabolizers (IMs), 145 normal metabolizers (NMs), and 6 ultrarapid metabolizers (UMs). Multiple linear regression analysis showed that CYP2D6 PMs had 92% higher duloxetine C/D-ratio compared with NMs ($P = 0.02$). CYP2D6 IMs or UMs did not have different C/D-ratio from NMs ($P > 0.07$). Age ≥65 years was associated with a 63% increase in C/D-ratio ($P = 0.004$), and women had 53% higher C/D-ratio compared with men ($P = 0.02$).

Conclusion: The present study shows that patients who are CYP2D6 PMs have almost 2-fold higher duloxetine exposure compared with NMs, and may benefit from a reduced starting dose to prevent concentration-dependent side effects. High age and female sex were also associated with increased duloxetine exposure.

Pharmacokinetic variability and markers of toxicity of sulthiame in patients with epilepsy

Msc Pharm Katrine Heger[1], Kari Kjeldstadli[2], Nelly Ring[2], Kari Modalsli Aaberg[3], Signe Flood Kjeldsen[4], Margrete Larsen Burns[4], Svein I Johannessen[4,5], Cecilie Johannessen Landmark[1,4,5]
[1]Program for Pharmacy, Faculty of Health Sciences, Oslo Metropolitan University, Oslo, Norway, [2]Section for Clinical Pharmacology, Department of Pharmacology, Oslo University Hospital, Oslo, Norway, [3]Division of Clinical Neuroscience, National Center for Epilepsy, Oslo University Hospital, Oslo, Norway, [4]Section for Clinical Pharmacology, The National Center for Epilepsy, Department of Pharmacology, Oslo University Hospital, Oslo, Norway, [5]The National Center for Epilepsy, Oslo University Hospital, Sandvika, Norway

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Purpose: Sulthiame is an old antiseizure medication (ASM), which is increasingly used to treat epilepsy in children and adults. The purpose was to investigate pharmacokinetic variability of sulthiame in children and adults with epilepsy, in relation to age, co-medication, dose, serum concentrations and measurements of biochemical markers of toxicity in a clinical setting, and to study how other ASMs may affect the metabolism of sulthiame.<

Method: Retrospective quantitative data from the therapeutic drug monitoring (TDM) database at the section for Clinical Pharmacology, the National Center for Epilepsy, Norway, was used. Data was collected from patients with epilepsy of all ages who were treated with sulthiame, 2015 – 2021. Variations in concentration/dose (C/D) and concentration/(dose/bodyweight) (C/(D/kg)) ratios were used as expressions of pharmacokinetic variability. In patients with at least five measurements, the coefficient of variation (CV) for C/D ratios for intrapatient variability was calculated.

Results: TDM data from 326 patients (127 female/199 male) were included, mean age 11.4 (range 2-44) years. Weight was stated in 86% of the patients (range 14-109 kg). The interindividual pharmacokinetic variability was notable, as illustrated by a 13-fold (0.013 – 0.173 µmol/L/mg) and 16-fold (0.52 – 8.40 (µmol/L)/(mg/kg) variability in C/D ratios and C/(D/kg) ratios, respectively. The intraindividual variability was up to 8-fold, and intrapatient CVs ranged from 10 to 78%. Simple linear regression demonstrated a statistically significant positive linear correlation (r2 = 0.25) between age and C/(D/kg) ratio (P<0.001). The sulthiame C/(D/kg) ratio was 3 times higher in adults (≥18 years) as compared to the youngest children (<6 years) (P<0.001)), reflecting a higher clearance. Patients using CYP-inducing ASMs (n=7; carbamazepine, phenytoin, phenobarbital, primidone), had a 30% lower sulthiame C/(D/kg) ratio as compared to patients using ASMs neutral to interactions, but the difference was not statistically significant. No statistically significant differences in sulthiame C/(D/kg) ratio were demonstrated for various ASM comedication groups, possibly due to the small number of patients in each comedication group. However, clobazam used in combination with sulthiame (n=28) resulted in a 3.5 times higher N-desmethylclobazam C/(D/kg) ratio than clobazam used with neutral comedication (n=45) (P < 0.001), indicating CYP2C19 inhibition by sulthiame. Patients with pH values below the reference range (n=15) had a 33% higher mean sulthiame serum concentration as compared to patients with blood gas values (pH, pCO2, base excess and HCO3) within the reference ranges (n=22), suggesting pH as a possible marker for sulhiame toxicity.

Conclusion: The study revealed extensive intra- and inter-individual pharmacokinetic variability of sulthiame, where age is a contributing factor. Based on the results, sulthiame is a potent inhibitor of the enzyme CYP2C19. Use of TDM and biochemical markers may contribute to individualized and safe treatment with sulthiame.

Optimising risperidone treatment in children with autism spectrum disorder: a therapeutic drug monitoring simulation study

MD Rebecca Hermans[1,2,3], BSc Alaya Storm[2], Dr. Sanne Kloosterboer[1], Prof.Dr. Manon Hillegers[1], Prof.Dr. Birgit Koch[2,3], Dr. Bram Dierckx[1], Dr. Brenda de Winter[2,3]
[1]Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Center, Rotterdam, Netherlands, [2]Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, Netherlands, [3]Rotterdam Clinical Pharmacometrics Group, Erasmus University Medical Center, Rotterdam, Netherlands

Psychiatry, Møterom 4, september 25, 2023, 13:00 - 14:30

Background
Risperidone is frequently prescribed to children and adolescents with autism spectrum disorder (ASD) and comorbid irritability and aggression. While often effective, risperidone use is also associated with serious side effects, most notably weight gain. In the SPACe study, we showed that sum trough concentrations of risperidone and its metabolite 9-hydroxyrisperidone are positively correlated to weight gain and effectiveness. In this study, we aimed to determine a target range for risperidone sum trough concentrations that balances weight gain with effectiveness. In addition, we simulated the effect of therapeutic drug monitoring (TDM) to optimise treatment.

Methods
In a retrospective cohort (n=24 patients) from the SPACe study, the therapeutic range for risperidone leading to the smallest increase in body mass index z-scores (BMIz) while still retaining effectiveness as measured by the irritability subscale of the Aberrant Behavior Checklist (ABC-I) was determined. Subsequently, the effect of TDM was simulated using a population PK model implemented in online software platform InsightRX. Dosing advice targeting the middle of the therapeutic range was based on blood concentration levels and administered dose at 12 weeks after start of treatment, after which resulting concentrations at 24 weeks were simulated and compared to observed concentrations.

Results
We found that a risperidone sum trough target range of 3.5-7 µg/L would minimise increase in BMIz and optimise effectiveness. Dosing advice using TDM and a population PK model would lead to a significantly larger proportion of patients achieving a concentration within the therapeutic range 24 weeks after start of treatment (62.5% vs 16.7%, p=.003). Furthermore, significantly fewer patients would have a concentration above the therapeutic range (29.2% vs 62.5%, p=0.43).

Conclusion
In this simulation study, TDM of risperidone significantly increased the amount of children and adolescents with ASD who reach a concentration within a set therapeutic range. TDM could be a useful tool in optimising risperidone treatment in this population.

A pooled population pharmacokinetic study of oral and intravenous clavulanic acid in neonates

MSc Stef Schouwenburg[1,2], MD Fleur Keij[3,4], Dr. Tim Preijers[1,2], Prof. Dr. Karel Allegaert[5], Dr. Gerdien Tramper-Stranders[3], Prof. Dr. Birgit Koch[1,2]
[1]Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, Netherlands, [2]Rotterdam Clinical Pharmacometrics Group, Erasmus University Medical Centre, Rotterdam, Netherlands, [3]Department of Paediatrics, Division of Neonatology, Rotterdam, Netherlands, [4]Department of Pediatrics, Franciscus Gasthuis & Vlietland, Rotterdam, Netherlands, [5]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium

Anti-infectives 2 - antibiotics and antifungals, Møterom 4, september 26, 2023, 13:00 - 14:30

Introduction
Infectious diseases are a major cause of childhood morbidity and mortality. Therefore, antibiotics are among the most commonly prescribed drugs for (pre-)term neonates. Beta-lactam antibiotics specifically are effective against bacterial infections through inhibiting cell wall synthesis. However, bacteria can develop resistance for beta-lactam antibiotics by producing beta-lactamase, an enzyme that inactivates the bacteriostatic effects and causes antibiotic degradation. To counter this effect, clavulanic acid, a beta-lactamase inhibitor, is often co-administered with amoxicillin or ticarcillin. Current dosing strategies focus mainly on the beta-lactam antibiotic component, with little attention paid to the clavulanic acid specific dosing regimens as no pharmacodynamic target for clavulanic acid is available yet. Currently, there is a lack of population-based studies to elucidate the pharmacokinetic properties of clavulanic acid in (pre-)term neonates.

Objectives
To describe clavulanic acid disposition following oral and intravenous administration in (pre-) term neonates. Additionally, the influence of covariates on clavulanic acid disposition and pharmacokinetic parameters will be assessed.

Methods
In this pooled population pharmacokinetic study two datasets from Rotterdam, the Netherlands (amoxicillin/clavulanic acid 4:1) and Durham, United States (ticarcillin/clavulanic acid 30:1) were combined. The complete cohort consisted of 60 (15 intravenous, 45 oral) (pre-)term neonates with a median (range) gestational age of 39.4 weeks (23 – 41.7), postnatal age of 40 days (6 – 44), and bodyweight of 3.4 kilograms (0.6 – 4.5). In total, 158 clavulanic acid blood concentrations (76 intravenous and 82 oral) were available for analysis. Postnatal age, gestational age, sex, and weight were tested in the model as covariates to explain the observed variability in pharmacokinetic parameters between patients. Data analysis was performed using nonlinear mixed-effects modeling with NONMEM v7.5 (ICON Development Solutions, Ellicott City, MD, USA). Simulations were performed using Markov Chain Monte Carlo methods.

Results
A one-compartment model with an additive residual error best described clavulanic acid pharmacokinetics. For a typical patient, the population estimates were 0.2 L/h/kg for clearance, 0.3 L for the volume of distribution and 14% for bioavailability. Clavulanic acid is absorbed with an estimated population absorption coefficient of 0.4 h-1. Inter-individual variability for clearance was estimated and resulted in an unexplained variability of 65.4% and shrinkage of 15%. Allometric scaling as well as other morphometric relationships were tested, but were not able to improve model fit. Incorporation of the covariates on clavulanic acid clearance did not further explain any variability. The percentage of free time above the minimal inhibitor concentration was simulated as a theoretical target for clavulanic acid pharmacodynamics.

Conclusion

This study described the first population pharmacokinetic analysis for oral and intravenous clavulanic acid in (pre-)term neonates. It was demonstrated that clavulanic acid bioavailability is lower in neonates compared with adults (14% vs. 60%, respectively). In order to further optimize clavulanic acid dosing regimens, future research should focus on a pharmacodynamic target to ensure treatment efficacy.

Preanalytical stability of 29 anti-infective agents in plasma and whole blood.

Dr Sophie Magreault[1], Dorine Pierredon[2], Judith Akinotcho - Relouzat[2], Dr Françoise Jaureguy[3], Pr Etienne Carbonnelle[3], Pr Vincent Jullien[1]
[1]Unité Fonctionelle De pharmacologie, GHU Paris Seine Saint-Denis, Ap-Hp, Université Sorbonne Paris Nord Et Sorbonne Paris Cité , Inserm, Iame , Bondy, France, [2]Unité Fonctionelle De pharmacologie, GHU Paris Seine Saint-Denis, Ap-Hp, Bondy, France, [3]Laboratoire De Microbiologie, GHU Paris Seine Saint-Denis, Ap-Hp, Université Sorbonne Paris Nord Et Sorbonne Paris Cité , Inserm, Iame, Bobigny, France

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

1. Introduction

Therapeutic Drug Monitoring (TDM) requires a validated assay, but also the use of appropriate conditions for samples' shipment and storage. Such conditions depend on the stability of the molecule to be analyzed. However, few stability data are currently available for anti-infective agents. The aim of this study was to evaluate the stability of 29 molecules in whole blood and plasma under different storage conditions.

2. Materials and Methods

The pre-analytical stability of 22 antibiotics (amoxicillin, aztreonam, cefazolin, cefepim, cefotaxime, cefoxitin, ceftazidime, ceftobiprole, ceftolozane, ceftriaxone, ciprofloxacin, clindamycin, cloxacillin, daptomycin, levofloxacin, linezolid, meropenem, metronidazole, moxifloxacin, piperacillin, sulfamethoxazole and trimethoprim), 2 beta-lactam inhibitors and 5 anti-tuberculosis drugs (ethambutol, isoniazid, rifabutin, rifampicin and pyrazinamide) was assessed in plasma up to 6h at room temperature (RT), 24h at +4°C, 1 month at -20°C and 6 months at -80°C. Their stability in whole blood was up to 24h at RT and 72h at +4°C. For each molecule, a control sample was prepared and processed immediately.

3. Results

For whole blood samples, meropenem concentration decreased by approximately 20% after 24h at RT and after 72h at +4°C. Cefotaxime and ciprofloxacin decreased by 20-25% after 72h at +4°C. All other antibiotics were stable under the tested conditions. In contrast, antituberculosis drugs, in particular isoniazid, were less stable in whole blood (stable for only 6h at RT and 24h at +4°C).
In plasma, all molecules were stable for 6 hours at room temperature and 24 hours at +4°C. Beta-lactams and isoniazid were stable for 5 days at -20°C but strongly degraded after 1 month. All molecules were stable for 6 months at -80°C.

4. Conclusion

The pre-analytical stability of a large number of anti-infective molecules is described. The present results can be used to determine appropriate shipment and storage conditions for the investigated molecules.

A Clinical Research Method for the Analysis of Antidepressant Drugs in Plasma using the Xevo TQD

Mr Stephen Balloch[1], PhD Lisa Calton[1], MSc Gareth Hammond[1], BSc Robert Wardle[1], PhD Andreas Lund Ertbjerg[2], MSc Godo Bosch[3]
[1]Waters Corporation, Wilmslow, United Kingdom, [2]Waters, Denmark, Taastrup, , [3]Waters S.A.S., Saint-Quentin En Yvelines Cedex, France

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Background: Depression is common globally, with an estimated 3.8% of the population affected. The condition can impact individuals' ability to function in work, social and family settings. Many antidepressant drugs are currently prescribed, encompassing selective serotonin reuptake inhibitors (SSRIs), serotonin-nonresponsive reuptake inhibitors (SNRIs) and tetracyclic antidepressants (TeCAs). However pharmacokinetic and drug interactions are known, therefore a reliable quantitative clinical research method may play a role in researching the effects of their administration.

Waters has developed a clinical research method for the following antidepressants in plasma; citalopram, desmethylfluoxetine, duloxetine, fluoxetine, fluvoxamine, O-desmethylvenlafaxine, sertraline and venlafaxine (10-1000 ng/mL); mirtazapine (5-500 ng/mL) and trazadone (30-3000 ng/mL).

Methods and materials: Matrix matched calibrators and QCs were prepared using in-house stocks and pooled plasma. Samples (50 µL) were treated with internal standard in acetonitrile. A water/methanol/ammonium acetate gradient was used with a Waters XSelect™ Premier HSS T3 Column on a Waters ACQUITY™ UPLC™ I-Class System followed by detection on a Xevo™ TQD Mass Spectrometer in a 5-minute run.

Results: No system carryover was observed following analysis of plasma samples containing the highest concentration calibrators. Analytical sensitivity investigations indicated precise quantification (≤20% CV, ≤17.6% bias) at concentrations equal to or lower than the lowest concentration calibrator. Total precision and repeatability were assessed (3 pools, 5 replicates, 5 days; n=25) and determined to be ≤10.0% RSD. Linearity experiments determined the method provided first or second order fits over the ranges analyzed; additionally, each run met acceptance criteria (coefficient of correlation ≥ 0.995, determined concentrations of calibrators ±15% of nominal, ±20% in the case of the lowest calibrator). Post-column infusion experiments demonstrated analytes eluted in regions free of major ion suppression or enhancement. Evaluation of matrix effects at low and high concentrations indicated compensation by the internal standard. Addition of high concentrations of several endogenous and exogenous materials did not affect quantification.
Conclusions: This quantitative method for clinical research demonstrates very good precision with minimal matrix effects and allows for the multiplexing of a panel of antidepressants in plasma in a short run time.

For Research Use Only. Not for Use in Diagnostic Procedures.

A Clinical Research Method for the Analysis of Immunosuppressant Drugs in Whole Blood using the Xevo TQ Absolute with Capitainer® B Devices

Mr Stephen Balloch[1], PhD Lisa Calton[1], MSc Gareth Hammond[1], BSc Robert Wardle[1], PhD Andreas Lund Ertbjerg[2], MSc Godo Bosch[3]
[1]Waters Corporation, Wilmslow, United Kingdom, [2]Waters, Denmark, Taastrup, Denmark, [3]Waters S.A.S., Saint-Quentin En Yvelines Cedex, France

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction: Traditional laboratory analysis of the immunosuppressant drugs cyclosporine, everolimus, sirolimus and tacrolimus is well-established in clinical research. However there remains a need for individuals to undergo an invasive, time-consuming and disruptive process under the supervision of trained staff in order to collect a sufficient volume of whole blood for laboratory analysis.

A reliable, remote sampling method may find utility in a clinical research setting. Here we describe the use of Capitainer® B Devices to obtain analytically sensitive, precise and accurate data for cyclosporine, everolimus, sirolimus and tacrolimus analysis using small sample volumes.
The Waters ACQUITY™ UPLC I-Class FL with Xevo™ TQ Absolute Mass Spectrometer was used to analyze these samples.

Materials and Methods: An in-house laboratory developed LC-MS/MS method to analyze all four immunosuppressants in a single run was developed. Waters MassTrak Immunosuppressant Calibrator and Control Sets (IVD) and whole blood External Quality Assurance samples (LGC, Bury, UK) were used in conjunction with Capitainer B devices to assess the performance of the method. Dried blood spots (10µL) were prepared using Capitainer B devices from initial 30 µL whole blood volumes, and the sample extracted using solvent containing internal standards. A water/methanol/ammonium fluoride gradient was used with a Waters C18 HSS SB column on a Waters ACQUITY™ UPLC™ I-Class and Xevo TQ Absolute Mass Spectrometer operating in positive electrospray ionization mode with run time of 1.5 minutes.

Results: Analytical sensitivity of the lowest calibrator at 1 ng/mL for everolimus, sirolimus and tacrolimus and 25 ng/mL for cyclosporine was demonstrated with S/N (PtP) > 10 across five analytical runs. We successfully demonstrated linearity of cyclosporine from 25-1500 ng/mL and everolimus, sirolimus and tacrolimus from 1-30 ng/mL, with r2>0.99 over five analytical runs. Total precision and repeatability across the four immunosuppressants (2, 8 and 22 ng/mL for everolimus, tacrolimus and tacrolimus; 150, 400 and 900 ng/mL for cyclosporine) with five replicates over five analytical runs (n = 25) was ≤7.6% CV. External quality assurance samples for all drugs met the scheme acceptance criteria, with mean bias ≤8.7%.

Conclusions: Using Capitainer B devices and very sample small volumes (30 µL of whole blood resulting in a 10 µL dried blood spot), an in-house laboratory method was used to meet validation goals for analytical sensitivity, linearity, precision and accuracy for cyclosporine, everolimus, sirolimus and tacrolimus. Furthermore, the advantages conferred by volumetric absorptive microsampling, notably removing the requirement for travel and a venous blood draw and facilitating home sampling, render this technique applicable to clinical research.

Capitainer are thanked for the provision of Capitainer B devices for this study.

A Simple Dilute and Shoot Method for the UPLC-MS/MS analysis of Pain Management Drugs and Drugs of Abuse from Urine for Forensic Toxicology

Mr Robert Wardle[1], Gareth Hammond[1], Mr Stephen Balloch[1], Dr Andreas Ertjberg[2], Mr Godo Bosch[3]
[1]Waters Corporation, Wilmslow, United Kingdom, [2]Waters Denmark, Taastrup, Denmark, [3]Waters S.A.S., Saint-Quentin En Yvelines Cedex, France

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction:
In the forensic toxicology laboratory, a sample will often be analysed using multiple methods to obtain a comprehensive view of the many drug classes. The analytical methods may include immunoassay, GC-MS and LC-MS/MS, to identify the drug classes, which typically includes illicit drugs and common drugs of abuse. Waters has developed a quantitative UPLC-MS/MS method for the unambiguous forensic toxicology identification of a large panel of these drugs.

Materials and Methods:
This method employs a simple sample extraction procedure using a dilute-and-shoot approach, coupled with rapid and reproducible chromatography, that achieves baseline separation for all critical pairs of potentially interfering analytes.

All standards were obtained from Cerilliant (Merck Life Sciences, Gillingham, UK), Toronto Research Chemicals (North York, ON) and Cambridge Bioscience (Cambridge, UK). Calibration standards and quality control (QC) materials were prepared by dilution of mixed stock solutions into pooled, blank urine. An internal standard working solution for all analytes (except clonazepam, dehydronorketamine, methedrone, noroxymorphone and α-pyrrolidinovalerophenone metabolite 1) was prepared in 50/50 (v/v) methanol/water at a concentration of 100ng/mL.

25µL of urine sample was transferred into a 96-well plate, internal standard added and mixed. Samples were diluted with a distilled water/formic acid solution, mixed and injected onto the Waters ACQUITY™ UPLC™ I-Class and Xevo TQ-S micro System operating in positive electrospray ionization mode with run time of 5.5 minutes.

Results:
All test analyte retention times were less than 4.6 minutes and either baseline chromatographic separation or mass selectivity ensured analytes did not interfere.

Three analyte dependent calibration ranges (high-range: 25–2,500ng/mL, mid-range: 10–1,000ng/mL and low-range: 2–200ng/mL) with corresponding QCs (high-range: 25, 75, 187.5 and 1875ng/mL, mid-range: 10, 30, 75 and 750ng/mL and low-range: 2, 6, 15 and 150ng/mL) were analysed with each batch. All calibration curve correlation coefficients (r2) were >0.99 and at least 75% of calibration points were within ±15% of their nominal value (±20% at the calibrator 1 level) except for N-desmethylzopiclone, norpropoxyphene and zopiclone. At least 66% of QC samples were within ±15% of their nominal value (±20% at the QC1 level) for all runs.

No significant carryover was observed with the exception of 7-aminoclonazepam and 7-aminoflunitrazepam. Matrix factor was between 0.85-1.15 for all analytes with the exception of phentermine and noroxymorphone. Analytical sensitivity was <20% CV for ten replicates of low level samples at or below the calibrator 1 concentration for all analytes except lorazepam, 6-acetylmorphine, α-hydroxyalprazolam, α-hydroxytriazolam, naloxone, naltrexone and pregabalin. Total precision and repeatability for each analyte was evaluated using 5 replicates of each QC over 5 occasions (n=25). For the majority of analytes, a precision acceptance criteria of ≤15.0% CV was achieved.

Discussion and Conclusions:
A fast dilute and shoot sample extraction has been successfully applied to the analysis of pain management drugs and drugs of abuse for forensic toxicology, using UPLC-MS/MS. Results were shown to be precise, with consistent matrix effects and minimal carryover for the majority of analytes within this large panel.

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Tramadol intoxication in children: a case report

Dr Guillaume Drevin[1], Dr Antoine BAUDRILLER, Séverine FEREC, Pr Nicolas PICARD, Pr Marie BRIET, Dr Chadi ABBARA
[1]CHU Angers, Angers, France

Toxicology -clinical and environmental, Sal C, september 26, 2023, 13:00 - 14:30

Introduction
Tramadol is a common painkiller used for the management of mild to moderately severe acute pain. It is a central analgesic that acts as a μ-opiate agonist but also as a serotonin and norepinephrine reuptake inhibitor. Tramadol is metabolized to O-desmethyltramadol (M1) mainly by the cytochrome P450 (CYP) 2D6 enzyme and to other metabolites by CYP3A4 and CYP2B6. In France, tramadol is the most dispensed opioid substance. However, using such a substance raises safety concerns, especially among children. In 2017, the U.S. Food and Drug Administration issued warning that recommends against use of codeine and tramadol in children younger than 12 years. In this context, the authors report the case of a tramadol overdose in a child.
Material and Methods
A 5-year-old male with a medical history of homozygous sickle cell disease has been hospitalized in pediatric intensive care unit for seizures and consciousness alteration. Toxicological investigations including blood alcohol concentration determination and general screening for the identification and quantification of prescription drugs, drugs of abuse, and toxicants were performed using several previously described validated methods. CYP2D6 genotype was determined using a Next Generation Sequencing plateform (MISeq, Illumina).
Results
Toxicological analysis highlighted the presence of tramadol and M1, respectively quantified in blood at 5.48 μg/mL and 1.32 μg/mL at admission, 0.77 μg/mL and 0.35 μg/mL 12 hours later, and 0.32 μg/mL and 0.18 μg/mL 20 hours later. The patient was predicted as CYP2D6 normal metabolizer (*35/*29).
Discussion and conclusion
Tramadol intoxication is rare in the pediatric population and only few cases have been reported in the literature. However, such cases are absolute emergencies that require hospitalization. Tanné et al. reported 7 pediatric cases of tramadol poisoning with ages ranging from 1 month to 15 years and 6 months. Regarding symptoms, in almost every case, respiratory failure and seizures were reported alongside with consciousness alterations. Except one case, intubation was always necessary. Naloxone was administered in 3 cases. Pediatric intensive care unit stay ranged from 1 to 4 days and tramadol blood level from 0.78 μg/mL to 5.51 μg/mL. Co-intoxication was also highlighted in 2 cases (paracetamol, zolpidem). The case reported here appear in agreement with these data. One of the most important difficulties with the use of tramadol in children relates to its pharmacokinetic (PK) properties. Indeed, tramadol PK is characterized by a great variability related to: i) volume of distribution (Vd) age variation; ii) CYP2D6 genetic polymorphisms. Such an issue is particularly relevant in intoxication cases. In the case reported here the plasma elimination half-life was estimated at 6.3 h, which appears significantly more than those reported in 2-8 year-old children (about 3 h). Further, here, this discrepancy does not seem related to genetic polymorphisms but more to the Vd. Indeed, the patient was predicted as CYP2D6 normal metabolizer (*35/*29). These results highlight the risk associated with the use of tramadol in children and the importance of considering PK variability among this population.

What dose of clindamycin should be administered by continuous infusion during combination therapy with rifampicin? A prospective population pharmacokinetics study.

Leo Mimram[1], Dr Sophie Magreault[2], Dr Younes Kerroumi[3], Dr Dominique Salmon[4], Dr Benjamin Kably[5], Dr Simon Marmor[3], Dr Anne-Sophie Jannot[6], Pr Vincent Jullien[2], Dr Valerie Zeller[7]
[1]Unité Fonctionnelle de Pharmacologie, GHU Paris Seine Saint-Denis, AP-HP, Bondy, France, [2]Unité Fonctionelle de Pharmacologie, GHU Paris Seine Saint-Denis, AP-HP, Université Sorbonne Paris Nord Et Sorbonne Paris Cité , Inserm, Iame, , France, [3]Centre de Référence des Infections Ostéo-Articulaires Complexes (CRIOAC), Groupe Hospitalier Diaconesses–Croix Saint-Simon, Paris, France, [4]Service de Médecine Interne, Hôpital Cochin, Assistance Publique–Hôpitaux de Paris (APHP), Paris, France, [5]Service de Pharmacologie DMU BioPhyGen, Hôpital Européen Georges-Pompidou, APHP, Paris, France, [6]Service d'Informatique Médicale, Biostatistiques et Santé Publique, Hôpital Européen Georges-Pompidou, APHP, Paris, France, [7]Service de Médecine Interne et Infectiologie, Groupe Hospitalier Diaconesses–Croix Saint-Simon, Paris, France

Anti-infectives 1 - antibiotics and antifungals, Sal B, september 25, 2023, 13:00 - 14:30

1.Introduction
Despite an important drug-drug interaction, it has been observed that clindamycin-rifampicin combination achieves effective plasma clindamycin concentrations, provided clindamycin is administered by continuous infusion. However, the precise clindamycin dosage remains unknown. The aim of the present study was to determine the daily clindamycin dosage to be administered by continuous infusion during combination therapy with rifampicin in order to achieve appropriate clindamycin plasma concentrations.

2. Material and methods
Data were prospectively obtained from 124 patients with BJIs who received clindamycin by continuous infusion, with 2 clindamycin concentrations measured for each patient. Twenty patients received clindamycin without rifampicin, 19 received clindamycin concomitantly with rifampicin and the remaining 85 received clindamycin successively without and with rifampicin. For these latter patients, clindamycin concentration was determined before and at least 10 days after rifampicin initiation. A population PK model was developed using NONMEM 7.5. Monte-Carlo simulations were run to determine the dosing regimens achieving clindamycin concentrations of at least 3 mg/L and within the 3-10mg/L target range.

3. Results
A linear one-compartment model with first-order elimination appropriately described the data. Clindamycin distribution volume was not estimated. Mean clindamycin clearance without and with rifampicin was equal to 10.9 and 33.6 L/h, respectively, with an interindividual variability (% CV) of 12.8%. The lowest daily clindamycin dosage achieving plasma concentrations of at least 3 mg/L in more than 90 % of the patients was 4200mg.

4. Discussion and Conclusion
Our results support the use of a daily clindamycin dosage of 4200mg/24h administered by continuous IV infusion, in case of rifampicin combination therapy. These high dose regimen needs individual TDM-guided dose adaptation.

Routine Therapeutic Drug Monitoring of Rivaroxaban: Experience at a Tertiary Center

Dr Paul Chin[1,2], Dr Adele O'Mahoney[2], Dr Isabel Hiskett[2]
[1]University Of Otago, Christchurch, New Zealand, [2]Te Whatu Ora Health New Zealaand - Waitaha Canterbury, Christchurch, New Zealand

Miscellaneous 2, Møterom 5, september 26, 2023, 13:00 - 14:30

Background: A liquid chromatography-mass spectrometry assay to determine plasma rivaroxaban concentrations has been available for routine clinical use at our tertiary institutions since 2017. The aim of the study was to describe (1) the use of the assay during July 2021 to March 2023; (2) the indications for testing; and (3) subsequent rivaroxaban prescribing decisions.

Methods: Patients for whom rivaroxaban concentrations were measured were identified using the laboratory database, and clinical data were extracted from the associated electronic health records.

Results: During the 22 months, there were 187 unique patients (female 54%) with median (range) age 75 (24-96) years that had 235 samples. The majority were anticoagulated for atrial fibrillation and treatment of venous thromboembolism, comprising 51% and 44%, respectively. The use of the rivaroxaban assay increased over time, with a mean (95% confidence interval) increase of +0.4 (0.1–0.7) samples per month. The median (range) rivaroxaban concentration was 78 (6-810) microg/L. The main reasons for testing were bleeding/thromboembolic event with rivaroxaban (22%), post-rivaroxaban initiation (22%), repeat sample post-rivaroxaban dose adjustment (11%), uncertainty about impact on renal function and drug-drug interactions (9%), concerning coagulation test result (7%). After the assay result, rivaroxaban dosing was decreased in 7% (17/235), increased in 3% (8/235), discontinued in 6% (15/235), continued in 79% (183/235) and unknown in 5% (12/235).

Conclusions: The clinical use of the rivaroxaban assay has increased, with 17% of results associated with a subsequent change in rivaroxaban prescribing.

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Clozapine treatment individualization: a joint pharmacokinetic/pharmacogentic approach

Dr Chadi Abbara[1], Dr Guillaume Drevin[1], Dr Guillaume Ifrah[2], Pr Nicolas Picard[3], Pr Bénédicte Gohier[2], Pr Marie Briet[1]

[1]Angers University Hospital - Pharmacology and Toxicology department, Angers, France, [2]Angers University Hospital - Psychiatry department, Angers, France, [3]Limoges University Hospital - Pharmacology and Toxicology department, Limoges, France

Psychiatry, Møterom 4, september 25, 2023, 13:00 - 14:30

Introduction:
Clozapine is atypical antipsychotic effective in treatment-resistant schizophrenia. The success or failure of clozapine therapy is affected by variates that impact clozapine pharmacokinetics (PK). The main variates explaining the inter-individual variabilities are cytochromes P450 (CYP). Among them, CYP 1A2 and 3A4 play a major role in clozapine metabolism whereas other CYP such as 2D6, 2C19, 3A5 had minor but not well explained role in clozapine metabolism. The main active metabolite is nor-clozapine. In this context, fluvoxamine, a CYP 1A2 inhibitor, may be used as a PK tool to modulate clozapine dose in order to decrease side-effects while maintaining efficacy. Here we present a case of clozapine dose individualization based on the use of fluvoxamine. The application of PK modelling and pharmacogenetics analysis (PGx) helped understanding the mechanisms implicated in clozapine disposition.
Materials and methods:
A 54 year-old woman, non-smoker, has been hospitalized with diagnosis of schizophrenia. The patient was unsuccessfully treated with two antipsychotics (risperidone, aripiprazole) Combination of clozapine-fluvoxamine appeared as the treatment of choice. For drug monitoring purpose, clozapine and its active metabolite, nor-clozapine, were quantified using LC/UV validated method. PK modelling by non-linear regression was realized by Monolix suites software (Lixoft). CYP 1A2, 2C19, 3A5, 3A4, 2D6 genotypes were determined by Next Generation Sequencing (MISeq, Illumina).
Results:
Following repeated doses of clozapine (50 mg BID) combined to fluvoxamine (50 mg QD) resulted in clozapine steady-state plasma concentration at 950 ng/mL (nor-clozapine 210 ng/mL). Considering the therapeutic range recommended by Hiemke et al. (Pharmacopsychiatry, 2018), administration was discontinued and clozapine plasma concentrations decreased slowly with a very high elimination half-life (~ 90 hr). When clozapine concentration attained 430 ng/mL (nor-clozapine 200 ng/mL), clozapine combined with fluvoxamine was administrated at the dose of 50 mg QD. Metabolic ratios (clozapine/nor-clozapine) ranged from ~4-5 (50 mg BID) to ~2-3 (50 mg QD). Repeated concentrations data were analysed by nonlinear regression. A one compartment with Michaelis-Menten elimination process was the best model to fit the data. PGx was realized in order to understand these PK and metabolism observations. The patient was predicted as a 2C9 intermediate metabolizer (*1/*2 genotype), 2D6 poor metabolizer (*4/*5 genotype) and 3A5 non-expressor (*3/*3). These results suggest the implication of other CYP isoforms than 1A2 and 3A4 in the metabolism of clozapine for this patient. Inhibition of 1A2 activity added to decreased activity of 2C9 and 2D6 with absence of 3A5 expression resulted in a non-linearity in the clozapine metabolism at low doses.
Conclusion:
These results confirmed the complexity of clozapine metabolism and disposition pathways. In addition, they highlight the importance of clozapine treatment individualization with respect to metabolic ratio and PGx. This example illustrates the benefits of applying a joint PK/PGx approach.

A comparison of free concentrations and fractions in vivo between unchanged form and active metabolite of itraconazole using UHPLC-MS/MS assay with equilibrium dialysis.

Mr. Motoshi Iwao[1], Dr. Ryota Tanaka[1], Dr. Yosuke Suzuki[2], Mr. Ryosuke Tatsuta[1], Dr. Takehiro Hashimoto[3], Prof. Kazufumi Hiramatsu[3], Prof. Hiroki Itoh[1]
[1]Department of Clinical Pharmacy, Oita University Hospital, Hasama-machi, Japan, [2]Department of Medication Use Analysis and Clinical Research, Meiji Pharmaceutical University, Kiyose, Japan, [3]Hospital Infection Control Center, Oita University Hospital, Hasama-machi, Japan

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Background: Itraconazole (ITCZ), a triazole antifungal agent, is metabolized to many metabolites, and hydroxyitraconazole (OH-ITCZ) is the major metabolite with antifungal activity comparable to ITCZ. Some retrospective reports have suggested that ITCZ exposure is related to efficacy and toxicity. On the other hand, a multicenter prospective study showed no relationship of plasma trough concentrations of ITCZ and/or OH-ITCZ with efficacy and toxicity. Protein-free (unbound) drug concentration has been reported to be a better biomarker for pharmacodynamics compared with total drug concentration. However, free fractions of ITCZ and OH-ITCZ in vivo are little known. In this study, we developed and validated an assay for quantification of total and free ITCZ and OH-ITCZ concentrations using ultra-high-performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-MS/MS) with equilibrium dialysis and compared in vivo free concentrations and free fractions between these compounds.
Methods: For measurement of free ITCZ and OH-ITCZ concentrations, plasma samples were subject to equilibrium dialysis, and the dialyzed samples were pretreated using a 96-well MCX µElution plate and analyzed by UHPLC-MS/MS. Adult patients who received oral or injective ITCZ between July 2016 and November 2022 at Oita University Hospital were recruited. The protocol for this study was approved by the Oita University Faculty of Medicine Ethics Committee (Review reference number: 2220) prior to study initiation.
Results: The assay fulfilled the requirements of the US Food and Drug Administration guideline for assay validation, with lower limit of quantification (LLOQ) of 10 ng/mL for total ITCZ and OH-ITCZ, and 0.025 and 0.25 ng/mL for free ITCZ and OH-ITCZ, respectively. Recovery rates of total ITCZ and OH-ITCZ from whole plasma ranged from 53.3% to 64.0%, while recovery rates of free ITCZ and OH-ITCZ from filtrated plasma ranged from 80.5% to 98.0%. Matrix effect varied between 79.1% and 109.4% for total ITCZ and OH-ITCZ, and between 91.3% and 119.2% for free ITCZ and OH-ITCZ. The assay was successfully applied to therapeutic drug monitoring of itraconazole in 11 patients (18 cases). Average free concentrations and free fractions in plasma were 0.188 ± 0.123 ng/mL and 0.024 ± 0.016% for ITCZ and 1.449 ± 1.017 ng/mL and 0.251 ± 0.109% for OH-ITCZ, respectively, indicating 7.7 and 10.5 fold higher for OH-ITCZ than for ITCZ.
Conclusions: Equilibrium dialysis minimizes non-specific adsorption of the analyte to the apparatus, and this characteristic is an advantage for the measurement of free ITCZ and OH-ITCZ compared with the previous ultrafiltration method. Using the developed quantitative method, we revealed that OH-ITCZ indicates a significantly higher free concentration in vivo than ITCZ. Taking OH-ITCZ having similar in vitro antifungal activity with ITCZ into consideration, OH-ITCZ could contribute more to the antifungal impact in vivo than ITCZ.

Simultaneous detection of blood concentration of CDK4/6 inhibitors and P-gp genetic polymorphism from a single dried blood spot

Dr Kei Irie[1,2], Mr Naoto Masuda[2], Dr Shuji Kishimoto[2], Dr Nobuyuki Muroi[1,3], Dr Tohru Hashida[1,2], Dr Shoji Fukushima[2]

[1]Department of Clinical Pharmacy Research, Center for Clinical Research and Innovation, Kobe City Medical Center General Hospital, Kobe, Japan, [2]Faculty of Pharmaceutical Science, Kobe Gakuin University, Kobe, Japan, [3]Department of Pharmacy, Kobe City Medical Center General Hospital, Kobe, Japan

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction: The dried blood spot (DBS) method is beneficial for pharmacokinetic investigations and precision dosing, which require accurate timing and multiple samplings. The advantages of the DBS method in pharmacokinetic studies include its straightforward sampling process and less invasive procedure as well as the analyte stability during sample storage. The DBS method has been used not only for measuring the blood concentration of drugs but also for genotyping. Determining the genotypes of metabolic enzymes and transporters and the blood levels from a single DBS would be useful for pharmacogenomic research and precision dosing. In this presentation, we describe the simultaneous detection of blood levels of CDK4/6 inhibitors (abemaciclib and palbociclib) and P-gp genetic polymorphisms (ABCB1, rs1045642) using a single DBS.

Materials and Methods: For DBS samples, 10 µL whole blood spiked with abemaciclib and palbociclib were pipetted onto filter paper (No. 2, 125 g/m2, Advantec, Tokyo, Japan) and dried for 2 h. Then, a 3 mm diameter DBS was cut out, added to 500 µL methanol containing abemaciclib-D8 and palbociclib-D8 as internal standards, and shaken for 30 min at room temperature in a 1.5 mL microtube. The supernatant (10 µL) was subsequently analyzed using LC-MS/MS (QTRAP 4500, AB Sciex, Framingham, MA, USA). Simultaneously, to perform genotyping for the P-gp genetic polymorphism (ABCB1, rs1045642) using a single DBS, DNA was extracted from the outside of the 3 mm punched out DBS using DBS extracta (Quantabio, Beverly, MA, USA). After adding 10 pg of the extracted DNA, real-time PCR was carried out using a TaqMan MGB Probe (Applied Biosystems, Assay ID: C___7586657_20). The results of genotyping using ten individual DBSs were compared with the results obtained using paired whole blood DNA extracted using the conventional column method (QIAamp DNA Blood Mini Kit, Qiagen).

Results: The calibration linear ranges of abemaciclib and palbociclib were 10–1,000 ng/mL, encompassing the therapeutic concentrations, and the accuracy, inter-assay precision, and intra-assay precision were within 15% of the quality control concentrations of 10, 20, 80, and 800 ng/mL. No matrix effects were observed in the ten individual DBS samples. The results of the genotyping of ABCB1, rs1045642 using leftover DBS were identical to those obtained using whole blood: four were wild type, two were mutant, and four were heterozygous.

Discussions and Conclusions: A method was successfully developed for simultaneous detection of CDK4/6 inhibitor blood levels and P-gp genetic polymorphisms from a single dried blood spot. Treatment with abemaciclib and palbociclib is frequently discontinued or terminated owing to adverse effects, such as severe neutropenia and diarrhea. If the relationship among these side effects, drug concentration, and genetic polymorphisms can be clarified using this method, it would be possible to propose a dosage plan suitable for individual patients.

Clinical consequences of infliximab immunogenicity and the impact of therapeutic drug monitoring: secondary analyses of a randomised clinical trial

MD Marthe Kirkesæther Brun[1,2], MD Kristin Hammersbøen Bjørlykke[2,3], MD, PhD Johanna E. Gehin[4], PhD David John Warren[4], PhD Rolf A. Klaasen[4], PhD Joseph Sexton[1], MD, PhD Øystein Sandanger[5], Prof Tore K. Kvien[1,2], MD, PhD Cato Mørk[6], Prof. Jørgen Jahnsen[2,3], MD, PhD Nils Bolstad[4], MD, PhD Kristin Kaasen Jørgensen[3], Prof. Espen A. Haavardsholm[1,2], MD, PhD Guro Løvik Goll[1], MD, PhD Silje Watterdal Syversen[1]

[1]Center for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, Oslo, Norway, , Norway, [2]Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [3]Department of Gastroenterology, Akershus University Hospital, Lørenskog, Norway, [4]Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway, [5]Section of Dermatology, Oslo University Hospital, Oslo, Norway, [6]Akershus Dermatology Center, Oslo, Norway

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction

Neutralising anti-drug antibodies (ADAb) are a problem in treatment with TNF-inhibitors (TNFi). Prospective data are needed to better understand how ADAb formation impacts safety and treatment outcomes of TNFi. Proactive therapeutic drug monitoring (TDM) allows for timely detection of ADAb and this strategy may have a role in reducing the negative clinical consequences of ADAb. The aim of the study was to explore the temporal relation between anti-infliximab antibody formation and treatment outcomes and adverse events, and to assess the impact of TDM as a strategy to reduce these consequences.

Materials and methods

Patients with immune mediated inflammatory diseases on infliximab therapy (n=615; 181 spondyloarthritis, 120 rheumatoid arthritis, 72 psoriatic arthritis, 114 ulcerative colitis, 83 Crohns disease and 45 psoriasis) were included in the Norwegian Drug Monitoring (NOR-DRUM) trials (1, 2) and randomised to TDM or standard infliximab therapy. Patients were followed for 30 and 52 weeks in the NOR-DRUM A (induction therapy) and NOR-DRUM B (maintenance therapy) trials, respectively. Neutralising ADAb were assessed with a drug sensitive automated fluorescence assay at each infusion. In this sub-study, we assessed the risk of; failure to achieve remission at week 30, disease worsening during 52 weeks of maintenance therapy, adverse events and treatment discontinuation in patients developing ADAb compared to patients without ADAb using logistic- or cox regression and Kaplan-Meier survival analyses, stratified by TDM or standard therapy. Regression analyses were adjusted for potential confounders (age, sex, diagnosis and use of immunosuppressive comedication). Remission and disease worsening were defined by disease specific composite scores (1, 2).

Results:

ADAb were detected in 147/615 (24 %) patients. Patients with ADAb had higher risk of not achieving remission 30 weeks after initiating infliximab therapy (odds ratio (OR) 2.4, 95 % confidence interval (CI) 1.3-4.2, P<0.01) and of having a disease worsening during 52 weeks of infliximab maintenance therapy (hazard ratio (HR) 2.1, CI 1.4-3.3, P<0.001). ADAb formation was not significantly associated with adverse events in general, but the risk of infusion reactions was highly increased in patients with ADAb (HR 29, CI 11-78, P<0.001). The risk of infliximab treatment discontinuation was increased in ADAb positive patients (HR 6.5, CI 4.7-8.9, P<0.001). Patients developing ADAb in the TDM group had lower risk of disease worsening (HR 0.4, CI 0.3-0.6, P<0.001) or an infusion reaction (HR 0.3, CI 0.1-0.7, P<0.01) than patients with ADAb in the standard infliximab therapy group. Patients with ADAb discontinued infliximab treatment more often in the TDM group than in the control group (HR 1.4, CI 1.0-1.8, P=0.03).

Discussions and conclusions:
Formation of ADAb led to poorer clinical outcomes both during induction and maintenance therapy with infliximab and increased the risk of infusion reactions. Early detection of ADAb by proactive TDM reduced the negative consequences of ADAb, both on infliximab effectiveness and safety, highlighting the role of proactive TDM in optimising TNFi therapy.

References:
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Development and validation of a method for the quantification of multi-class pesticides in hair by liquid chromatography - mass spectrometry

Eloïse Brillard[2], Camille Larrue[2], Antoine Dupuis[2,3], Pharmd, Phd Sandrine Lefeuvre[1,2]
[1]Laboratory of Toxicology and Pharmacokinetic , CHU Poitiers, INSERM CIC 1402, Poitiers, France, [2]CNRS 7267 EBI, University of Poitiers, Poitiers, France, [3]Pharmacy, CHU Poitiers, INSERM CIC 1402, Poitiers, France

Toxicology -clinical and environmental, Sal C, september 26, 2023, 13:00 - 14:30

1. Introduction

Pesticides were proved to cause multiple adverse health effects ranging from dermal to neurotoxicity, endocrine disruptors, cancers, etc…hence the need to develop an appropriate approach for biomonitoring in human matrices. Hair, a non-invasive sample, allows the detection of analytes in a broader time-window than other biological matrices (blood, urine) and is ideally suited for exposure measurement. The aim of this work was to develop and validate an analytical method for the quantification in hair of 70 pesticides and metabolites belonging to different chemical families (neonicotinoids, azoles, organophosphates, carbamates, organochlorines) by liquid chromatography - mass spectrometry (UHPLC-MS/MS).

2. Materials and Methods

Several washing procedures were evaluated for their ability to remove artificially deposited pesticides (different chemical classes) from hair surface : five organic procedures: acetone, dichloromethane, ethylacetate, methanol, acetonitrile; and three aqueous: water, acidified water, sodium dodecylsulfate (SDS). After decontamination, hair was dried and cut into 1-3 mm segments. Extraction process was done with QuEChERS in methanol. After evaporation of supernatant under nitrogen stream, dried sample was suspended in 100 µL of mobile phase. Analytical separation is performed in 15 min with a mobile phase gradient (Phase A: acidified buffered water; Phase B: acidified buffered methanol) on C18 Luna Omega Polar column (100mm x 2,1mm; 1,6 µm; Phenomenex). Samples were analyzed on a UHPLC-SM/SM (Qtrap6500; Sciex) in Multiple Reaction Monitoring (MRM) mode with an electrospray ionization interface (positive and negative). This method was then validated in accordance to European Medicines Agency recommendations. Four control levels (QCs) distributed over calibration range were prepared by spiking the hair with a pesticide stock solution. The parameters evaluated were: limit of detection (LOD), limit of quantification (LOQ), intra- and inter-day precision/accuracy (n=6), carry-over and matrix effects (ME) with the quantitative approach (n=6).

3. Results

The most effective washing solvent was water and SDS. After a washing procedure with successively water, SDS and water (10 min bath under with agitation), the 70 externally deposited pesticides were removed. The final procedure did not affect the chemicals biologically incorporated, as hair strands naturally containing pesticides were used. All compounds were quantified with a linear or quadratic regression between 2 and 100 pg/mg of hair ($r^2 > 0.997$). Overall precision and accuracy did not exceed 20% at LOQ and 15% for the others QC levels. ME studied at two concentration levels (low and high) presented CVs between 11 and 34 %. MEs due to ion enhancement was corrected by the addition of labeled internal standards. With a needle rinse before and after sample injection, no carry-over was observed.

4. Discussions and Conclusions

The QuEChERS method allows the extraction of a wide range of pesticides and metabolites from different chemical classes in hair with optimal sensitivity, precision and inaccuracy. The current panel can easily be extended with other compounds as the sample preparation and chromatography have been adapted for the quantification of different pesticide families. This easy to implement protocol will contribute to the knowledge of health risks related to the use of pesticides.

Population Pharmacokinetics and Dosing Optimization of Ceftazidime in Term Asphyxiated Neonates during Controlled Therapeutic Hypothermia

Msc Marlotte van der Veer[1], Timo de Haan[2], Linda Franken[1], Caspar Hodiamont[3], Floris Groenendaal[11], Peter Dijk[4], Willem de Boode[5], Sinno Simons[6], Koen Dijkman[7], Henrica van Straaten[8], Monique Rijken[9], Filip Cools[10], Debbie Nuytemans[2], Anton van Kaam[2], Yuma Bijleveld[1], Ron Mathôt[1]
[1]Department of Hospital Pharmacology & Clinical Pharmacology, Amsterdam University Medical Center, Amsterdam, Netherlands, [2]Department of Neonatology Emma Children's Hospital, Amsterdam University Medical Center,, , Amsterdam, Netherlands, [3]Medical Microbiology, Amsterdam University Medical Center, Amsterdam, Netherlands, [4]University Medical Center Groningen, Beatrix Children's Hospital, Department of Pediatrics, Division of Neonatology, Gronigen, Netherlands, [5]Department of Neonatology, Radboud University Medical Center, Radboud Institute for Health Sciences, Amalia Children's Hospital, Nijmegen, Netherlands, [6]Department of Pediatrics, Division of Neonatology, Erasmus MC-Sophia Children's Hospital, Rotterdam, Netherlands, [7]Department of Neonatology, Máxima Medical Center Veldhoven, Veldhoven, Netherlands, [8]Department of Neonatology, Isala Clinics, Zwolle, Netherlands, [9]Department of Neonatology, Leiden University Medical Center, Leiden, Netherlands, [10]Department of Neonatology, Vrije Universiteit Brussel, Brussels, Belgium, [11]Department of Neonatology, Wilhelmina Children's Hospital, Utrecht, Netherlands

Anti-infectives 2 - antibiotics and antifungals, Møterom 4, september 26, 2023, 13:00 - 14:30

Hypoxic-ischemic encephalopathy (HIE) due to perinatal asphyxia is a serious clinical condition with considerable morbidity and mortality rates in term neonates. Controlled therapeutic hypothermia (TH) is currently the standard of care for neonates suffering from moderate to severe HIE. Antibiotics are frequently prescribed in asphyxiated neonates directly after birth and during controlled TH as perinatal infections cannot be reliably ruled out as a possible cause of asphyxia. Antibiotic pharmacokinetics (PK) may be altered during controlled TH due to pathophysiological changes, such as altered hepatic- and renal clearance. Little is known about the PK properties of ceftazidime in neonates during controlled TH. We aimed to describe the population pharmacokinetics of ceftazidime in asphyxiated neonates during hypothermia, rewarming and normothermia and proposed a population-based rational dosing regimen with optimal PK/pharmacodynamic (PD) target attainment.

Data were collected in the prospective observational multicenter PharmaCool Study. A population PK model was constructed and probability of target attainment (PTA) was assessed during all phases of controlled TH using targets of 100% of the time that concentration in blood exceeds the minimum inhibitory concentration (T>MIC for efficacy purposes and 100%T>4xMIC and 100%T>5xMIC to prevent resistance for Pseudomonas aeruginosa). The PTA was calculated for different dosing regimens and a PTA of ≥90% was considered optimal.

A total of 35 patients with 338 ceftazidime concentrations were included. An allometrically scaled one-compartment model with postnatal age and body temperature as a covariate on clearance was constructed. For a typical patient receiving the current dose of 100 mg/kg/day in two doses and assuming a worst-case MIC of 8 mg/L for P. aeruginosa, PTA was 99.7% for 100%T>MIC during hypothermia (33.7 °C, PNA 2 days). PTA decreased to 87.7% for 100%T>MIC during normothermia (36.7 °C, PNA 5 days). Therefore, a dosing regimen of 100 mg/kg/day in 2 doses during hypothermia and rewarming and 150 mg/kg/day in 3 doses during the following normothermic phase is advised. Higher dosing regimens (150 mg/kg/day in 3 doses during hypothermia and 200 mg/kg/day in 4 doses during normothermia) could be considered when achievement of 100%T>4xMIC and 100%T>5xMIC is desired.

Double absorption gamma model for mycophenolic acid and systemic lupus erythematosus pediatric patients using a stochastic approximation expectation-maximization algorithm

PharmD Kévin Koloskoff[1], PhD Lucie Chambon[2], PhD Sylvain Benito[2], MD PhD Evelyne Jacqz-Aigrain[3], PharmD PhD Jean-Baptiste Woillard[1]
[1]Inserm, University of Limoges, CHU Limoges, P&T, U1248, France, [2]Exactcure, , France, [3]Université Paris Cité, Department of Pharmacology and Pharmacogenetics, France

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction: Mycophenolic acid (MPA), the active metabolite of mycophenolate mofetil (MMF), is widely used in the treatment of systemic lupus erythematosus (SLE). It has been shown that its therapeutic drug monitoring based on the area under the curve (AUC) improves treatment efficacy. MPA exhibits a complex bimodal absorption and a double gamma distribution model has been already proposed to accurately describe this phenomenon. These previous population pharmacokinetics models (POPPK) have been developed using Iterative Two stage Bayesian (IT2B) or Non-Parametric Adaptive grid (NPAG) methods. However, non-linear mixed effects (NLME) approaches based on SAEM algorithms have never been published so far for this particular model. The objectives of this study were (i) to implement the double absorption gamma model in Monolix, (ii) to compare different absorption models to describe the pharmacokinetics of MMF and (iii) to develop a limited sampling strategy (LSS) to estimate AUC in pediatric SLE patients.
Material & Methods: A data splitting of full pharmacokinetic profiles sampled in 67 children extracted either from the expert system ISBA (n=34) or the hospital Saint Louis (n=33) was performed into train (75%) and test (25%) sets. A POPPK was developed for MPA in the train set using a NLME based on the SAEM algorithm and different absorption models were implemented and compared (first order, transit or simple and double gamma distribution). The best three blood samples limited sampling strategy (LSS) was then determined in the test set using a Maximum-A-Posteriori Bayesian method to estimate individual PK parameters. Then the AUC based on the LSS was compared to the “true” AUC calculated using the trapezoidal rule applied on all samples and performances were assessed in the test set.
Results: Mean patient age and dose was 13 years old (5 – 18) and 18.1 mg/kg (7.9 – 47.6) respectively. 764 MPA concentrations from 107 occasions were included in the analysis. A double gamma absorption with a first order elimination from the central compartment best fitted the data. Goodness-of-fit plots and visual predictive check did not show any trend or bias. Using analytical solution of gamma distribution model instead of classical transit absorption models as implemented in Monolix also decreased the computational time from 12,600 seconds to 25.4 seconds. The optimal LSS with samples at 30 min, 2h and 3h post-dose exhibited good performances in the test set (mean bias -0.32% and RMSE 21.0%).
Discussions and Conclusion: The double absorption gamma model developed with the SAEM algorithm showed very accurate fit and reduced computational time. The POPPK developed in this study adequately estimated the MPA AUC in pediatric patients with SLE based on 3 samples. That paves the way for a larger use of this model to describe complex absorption process.

Quetiapine galore? Doses, diagnoses and serum concentrations of Norwegian quetiapine users 2001-2019 in a therapeutic drug monitoring material

Mr. Håvard Breivik[1,2], Dr. Andreas Austgulen Westin[2,1], Professor Lars Slørdal[1,2], Dr. Joachim Frost[2,1]
[1]Norwegian University of Science and Technology, Trondheim, Norway, [2]St. Olav University Hospital, Trondheim, Norway

Psychiatry, Møterom 4, september 25, 2023, 13:00 - 14:30

1. Introduction
Quetiapine has become the most commonly prescribed antipsychotic on the Norwegian market since its introduction in 2001. Over the past decade, reports have surfaced from numerous countries of widespread off-label use of quetiapine, and there are indications that such use now constitute the majority of quetiapine prescriptions in many countries. We wanted to investigate how changes in quetiapine prescription practices over these past 20 years are reflected in data from therapeutic drug monitoring analyses of quetiapine.

2. Materials and Methods
Requisitions and results for serum analyses of quetiapine at our department of clinical pharmacology in the period 2001-2019 (N=24,575) were processed and analyzed for trends in demographics, dosage, concentration levels and diagnoses indicating reimbursable use.

3. Results
The annual number of quetiapine serum samples analyzed increased towards a peak of 1535 samples in 2011, followed by a decline towards 721 in 2019. Females constituted 57,9% of the study population. Reported daily doses of quetiapine decreased by 20 mg per unique patient per year throughout the study period. Among samples collected using proper sampling procedure, the corresponding dosage decrease was 24 mg per year. A similar trend was not seen in measured serum concentrations, and there was only a moderate degree of linear correlation between doses and serum concentrations ($r=0.404$, $p<0,001$). The proportion of unique patients with requisitions containing text indicating reimbursable use was 13,1% for the whole study period, peaking at 27,9% in 2006. Patients where the requisitions indicated reimbursable use used on average 100 mg higher daily dose than the non-reimbursable group.

4. Discussions and Conclusions
The trend towards lower daily quetiapine doses may reflect increasing off-label use. The observation that serum concentrations did not decrease correspondingly may be related to e.g. increased adherence, interference from intoxication cases, and/or a possible reduction in additional “as needed” doses. The proportion of patients with information of reimbursable diagnoses was lower than expected in a TDM population.

To our understanding, these results provide additional documentation of increasing low-dose usage of quetiapine, and signal both increasing off-label use, as well as possibly higher dose-intake than prescribed and incorrect filing of reimbursable use in this population. There is a continued need for characterization and investigation of quetiapine use and prescription practices, and the extent of and motivations for off-label prescription of the drug.

Predictive Performance of a Gentamicin Pharmacokinetic Model in Term Asphyxiated Neonates undergoing Controlled Therapeutic Hypothermia

Msc Marlotte van der Veer[1], Timo de Haan[2], Linda Franken[1], Floris Groenendaal[3], Peter Dijk[4], Willem de Boode[5], Sinno Simons[6], Koen Dijkman[7], Henrica van Straaten[8], Monique Rijken[9], Filip Cools[10], Debbie Nuytemans[2], Anton van Kaam[2], Yuma Bijleveld[1], Ron Mathôt[1]
[1]Department of Hospital Pharmacology & Clinical Pharmacology, Amsterdam UMC location University of Amsterdam, , Netherlands, [2]Department of Neonatology, Emma Children's Hospital, Amsterdam University Medical Center, Amsterdam, The Netherlands, [3]Department of Neonatology, Wilhelmina Children's Hospital, Utrecht, The Netherlands, [4]University Medical Center Groningen, Beatrix Children's Hospital, Department of Pediatrics, Division of Neonatology, University of Groningen, Groningen, The Netherlands, [5]Department of Neonatology, Radboud University Medical Center, Radboud Institute for Health Sciences, Amalia Children's Hospital, Nijmegen, The Netherlands, [6]Department of Pediatrics, Division of Neonatology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands, [7]Department of Neonatology, Máxima Medical Center Veldhoven, Veldhoven, The Netherlands, [8]Department of Neonatology, Isala Clinics, Zwolle, The Netherlands, [9]Department of Neonatology, Leiden University Medical Center, Leiden, The Netherlands, [10]Department of Neonatology, Vrije Universiteit Brussel, Belgium

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction

Model validation procedures are crucial when population pharmacokinetic (PK) models are utilized to develop dosing algorithms and to perform therapeutic drug monitoring. Ideally, external generalizability of a population PK model is evaluated with independent data. We have previously published a population PK model describing the PK of gentamicin in term asphyxiated neonates during controlled hypothermia, which showed altered gentamicin clearance during the hypothermic phase. Based on simulations in this specific patient population, an empiric dose of 5 mg/kg every 36 h or every 24 h for neonates with gestational age 36-40 and gestational age 42 weeks is advised. In the current study, the predictive performance and generalizability of this model is assessed using an independent dataset of asphyxiated neonates undergoing controlled hypothermia.

Methods

The external dataset contained neonates included in the prospective observational multicenter PharmaCool Study. Within this study, body temperature was lowered to 33.5 °C for 72 hours within 6 hours of the hypoxic ischemic incident, after which neonates were rewarmed to normothermia (36.5 °C). Blood samples were drawn at fixed time points during hypothermia (day 2 and 3), rewarming (day 4) and normothermia (day 5). Predictive performance was assessed by visual inspection of observed-versus-predicted plasma concentration plots and calculation of bias and precision. Additionally, simulation based diagnostics, model refitting and bootstrap analysis were performed.

Results

The external dataset included 323 gentamicin concentrations of 39 neonates. The vast majority of neonates in the external dataset were treated at different centers compared to the original dataset. Weight (median: 3170 grams (range: 2260-4620) and gestational age (median: 40 weeks (range: 36-42) were comparable between neonates included in the original and the external dataset. The original gentamicin PK model predicted the observed gentamicin concentrations with reasonable accuracy and precision during all phases of controlled therapeutic hypothermia. For all gentamicin concentrations, the mean prediction error (MPE) was 0.14 mg/L (95% CI: 0.07 – 0.23) and the root mean square error (RMSE) was 0.74 mg/L (95% CI: 0.64 – 0.84). During the normothermic phase slightly more overprediction occurred in trough levels as compared to the hypothermic phase, but was deemed acceptable as 80% of gentamicin samples were drawn in the hypothermic phase (normothermia MPE: 0.44 mg/L (95% CI: 0.30 – 0.58), RMSE: 0.86 (95% CI 0.26 – 1.47) versus

hypothermia MPE: 0.18 mg/L (95% CI: 0.10 – 0.26), RMSE: 0.83 (95% CI 0.57 – 0.90)). Model appropriateness was confirmed with prediction corrected visual predictive checks and normalized prediction distribution error analyses. Model refitting to the combined dataset (n=86 neonates with 935 samples) showed accurate estimation of PK parameters.

Discussion and Conclusion

We demonstrated that the previously published gentamicin PK model in neonates was able to adequately predict gentamicin concentrations during all phases of controlled therapeutic hypothermia. These results justify the generalizability of the gentamicin dosing recommendations done in the original study and its applicability in therapeutic drug monitoring.

Personalized tacrolimus dosage by model-based Bayesian Prediction in renal transplant recipients. A prospective controlled randomized clinical trial.

Dr Nuria Lloberas[1], Prof Pharm D PhD Helena Colom[2], PhD Anna Vidal-Alabró[1], PhD Pere Fontova[1], PhD Raul Rigo[3], PhD Ariadna Padró[3], MD PhD Edoardo Melilli[1], MD PhD Núria Montero[1], MD PhD Ana Coloma[1], MD PhD Anna Manonelles[1], MD PhD Alex Favà[1], MD PhD Oriol Bestard[1], MD PhD Maria Meneghini[1], MD PhD Joan Torras[1], Prof MD PhD Josep M Cruzado[1], Prof MD PhD Josep M Grinyó[1]
[1]Nephrology Service, Bellvitge University Hospital - IDIBELL, Barcelona, Spain, [2]Department of Pharmacy and Pharmaceutical technology and Physical-chemistry, Biopharmaceutics and Pharmacokinetics Unit, School of Farmacy and Food Sciences, University of Barcelona, Barcelona, Spain, [3]Biochemistry Department,Bellvitge University Hospital - IDIBELL, Barcelona, Spain

Immunosuppression 1, Sal D, september 25, 2023, 13:00 - 14:30

For three decades, tacrolimus (Tac) dose adjustment in clinical practice has been calculated empirically according to the manufacturer's labeling based on a patient's body weight. Our group developed and validated a Population pharmacokinetic (PPK) model including pharmacogenetics (cluster CYP3A4/CYP3A5), age, and hematocrit. This study aims to assess the clinical applicability of this PPK model in the achievement of Tac C0 compared to the manufacturer's labeling dosage.

A prospective two-arm, randomized, clinical trial was conducted to determine Tac starting and subsequent dose adjustments in renal transplant recipients. Ninety-six patients were enrolled and randomly allocated into two groups. Control group received the first Tac dose according to the manufacturer’s dosing recommendations based on body weight. Subsequent Tac doses were adjusted considering Tac pre-dose concentration target as clinical routine practice. For PPK group, Tac initial doses were calculated using our previous algorithm from the PPK model. Subsequent doses were then adjusted by applying a model-based Bayesian prediction considering the ongoing C0, CYP3A4 and CYP3A5 cluster polymorphisms, age, and hematocrit. All pre-dose concentrations and changes in doses within 90 days of follow-up were collected for both groups.

A higher proportion of patients (54.8%) in thePPK group achieved the Tac therapeutic target compared to the 20.8% of control group. The 30% superiority margin in target C0, established as a primary endpoint, was significantly fulfilled (33.9%, CI 95%: 13.9% - 53.9%; P = 0.0011). Sensitivity analysis with a narrower therapeutic range defined as 6-8 ng/ml corroborated significant differences between control and PPK groups concerning the percentage of patients in target 20.8% vs 40.5%). After the first Tac dose, patients from PPK group were less over-exposed compared to the control group (14.3% vs 45.8%, P = 0.0126). In contrast, no statistical differences were observed related to Tac under-exposure between groups. PPK patients showed less intra-patient variability (CV=22.9, IQR 19.2-29.4, range 12.4-54.3 versus CV=31.2, IQR 23.7-43.7, range 9.6-70.5; P < 0.0023) compared to the control group. PPK patients reached sooner Tac C0 target (5 d (IQR 5-10; range 5-15) vs 10 d (IQR 10-30; range 5-90), P = 0.0002) and required fewer Tac dose modifications (0.5±0.67 vs 1.78±1.41, P <0.0001) compared to the control group within 90 days after renal transplant. There was a lower percentage of patients with DGF in the PPK group than in the control group (27.5% vs 46.7%, P = 0.078) with a mean length of (2.09±1.45 vs 7.19±7.41) days respectively (P = 0.113). Likewise, there was a trend for a shorter duration of DGF in the PPK group than in the control group (median 1, IQR 2, min-max 1-5 versus median 4, IQR 10.5, min-max 0-21, respectively, P = 0.125). No statistically significant differences were observed in the incidence of NODAT between PPK and the control group (12.5% vs 6.7%, P = 0.466) and trembling episodes (17.5% vs 24.4%, P = 0.569).

PPK-based Tac dosage offers significant superiority for starting Tac prescription over the classical labeling-based dosage according to the body weight, which may optimize Tac-based therapy from the first days after transplantation.

Real-life pharmacokinetic data of mycophenolic acid and model based calculation of area-under-the-curve in a pediatric population with different renal diseases

Carsten Müller[1], PhD Pedram Omrani[1,2], Dr. Silke Gastine[4], Dr. Agnes Hackl[2], Dr. Nieko Punt[5], Prof. Martin Hellmich Hellmich[3], MD Rasmus Ehren[2], MD Martin H. J. Wiesen[1], Prof. Lutz T Weber[2]
[1]Pharmacology at the Laboratory Diagnostics Centre, Department of Therapeutic Drug Monitoring, University Hospital of Cologne, Cologne, Germany, [2]Pediatric Nephrology, Children's and Adolescents' Hospital, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany, [3]Institute of Medical Statistics and Computational Biology, Faculty of Medicine and University Hospital Cologne, Cologne, Germany, [4]Great Ormond Street Institute of Child Health, University College London, London, United Kingdom, [5]Medimatics, 6229 HR Maastricht, The Netherlands University Medical Center Groningen, Department of Clinical Pharmacy, Maastricht, The Netherlands

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Here we investigated the pharmacotherapy with MPA in 511 patients in a retrospective single-center observational investigation on therapeutic drug monitoring in a real-life
clinical approach with a predominant number of renal diseases and a small number of non-renal diseases. MPA PK sampling was performed on at trough (C0) and peak
timepoints 30 minutes after intake (C1)and 120 minutes after intake (C2) of the drug. MWPharm++ was used for individual calculation of MPA-AUC0-12h and for the
parameter estimates (clearance and distribution volumes) and apparent elimination half-life. A population pharmacokinetic analysis (PopPK) was performed using NONMEM (version 7). Model evaluation was performed using bootstrap analysis, predictioncorrected visual predictive check (pcVPC), as well as standardized visual predictive check (sVPC). MPA concentration data fitted best to a two-compartment model with a proportional-error model and total clearance, central compartment volume,
intercompartment clearance, and volume of distribution at steady-state were investigated. Population mean estimates of MPA clearance (CL), inter-compartmental clearance (Q), volumes of distribution in the central (Vc) and peripheral compartments (Vdss),
absorption rate constant (Ka) and lag-time (ALAG1) were CL = 15.8 L/h(95% CI, 3.7 to 27.9), Q = 41.9L/h (95% CI,37.0 to 46.8), Vc = 26.8 L (95% CI, 23.5 to 30.1), Vdss = 206 L (164.6 to 247.4), Ka= 5.16 h-1 and ALAG1 = 0.215 h respectively. Inclusion of creatinine-clearance, leucocytes and type of disease reduced the inter-individual variability in CL from 65.9% to 56.9%. Moreover, calculation of MWPharm++ derived MPA-AUC0_12hMWPHARM and NONMEM derived MPA-AUC0-12hNONMEM showed distinctly high correlation with r2= 0.865.

Comparison of three renal function formulas for Ganciclovir/Valganciclovir dose individualization using a population approach in CMV transplant patients

PhD Panagiotis Nikolaos Lalagkas[2], PhD Jorge Iliou[2], PhD Raul Rigo[3], MD PhD Oriol Bestard[1], Prof MD PhD Josep M Cruzado[1], MD PhD Edoardo Melilli[1], MD PhD Joan Torras[1], PhD Beatriz Fernández-Alarcon[2], Prof MD PhD Josep M Grinyó[1], Prof PhD Helena Colom[2], Dr NURIA LLOBERAS[1]
[1]Nephrology Service, Bellvitge University Hospital - IDIBELL, Barcelona, Spain, [2]Department of Pharmacy and Pharmaceutical technology and Physical-chemistry, Biopharmaceutics and Pharmacokinetics Unit, School of Farmacy and Food Sciences, University of Barcelona, Barcelona, Spain, [3]Biochemistry Department,Bellvitge University Hospital - IDIBELL, Barcelona, Spain

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Background: Ganciclovir (GCV) and valganciclovir (VGC) are the gold standard treatments for cytomegalovirus (CMV) infection or prevention in solid organ transplantation (SOT), both adjusted to renal function. Both show high interindividual pharmacokinetic variability, mainly due to the large variety of both renal function and body weight (BW). Therefore, accurate estimation of renal function is crucial for GCV dose optimization. This study aimed to assess actual dose recommendations through a newly developed population pharmacokinetic model using Chronic Kidney Disease EPIdemiology collaboration [CKD-EPI]) the formula for estimating renal function.

Methods: Sixty Caucasian patients with established CMV infections undergoing allogeneic solid organ transplantation (kidney, n=45; heart, n=10; liver, n=5) were included. The final dataset used consisted of 650 GCV concentrations. A population pharmacokinetic (PopPK) analysis was performed using NONMEM 7.4. Three formulas for estimating renal function were tested (Crokroft-Gault, MDRD, and CKD-EPI). Pharmacokinetic parameters were allometrically scaled to BW. A two-compartment open linear model with a time-lagged first-order absorption process, parametrized in terms of total GCV CL, Vc, Vp, CLD, first-order absorption rate constant (Ka), bioavailability (F), and lag time, best described the data. Between-patient variability (BPV) was included in CL, Vc, Vp, Ka, and F. Once the best model for predicting GCV exposure was selected based on statistical and clinical criteria, simulations were performed to evaluate the actual prophylaxis VGC dosage recommendations for different cutoffs of renal function (from 10 to 69 mL/min) and bodyweights (40, 70 and 100 kg). New doses were calculated based on exposure values given by the area under the plasma concentration-time curve (AUC) of 40-50 (mg/L)·h.

Results: CKD-EPI was identified as the best predictor of between-patient variability in GCV clearance. Overexposure was observed at the lowest renal functions that were decreased as renal function increased. New dose recommendations should be established for low renal function groups (10-19, 20-24, and 25-29 mL/min), particularly for BW of 40-70 kg. New initial dose requirements estimated from the new CKD-EPI model, were in general lower than those actually used, except for 25-39 mL/min and 81 to 130 kg, 50-59 mL/min, and 101-130 kg and 60-69 mL/min and 40-80 kg, cutoffs.

Conclusions: The CKD-EPI renal function estimate correlates the best with GCV clearance. The refinement of our previous PopPK model based on a more accurate estimation of renal function by CKD-EPI formula and BW as the size metric most used in the clinical practice can lead to refine initial dose recommendations and contribute to GCV and VGCV dose individualization when required in the prevention or treatment of CMV infection in SOT patients. The new model can i) increase the accuracy of GCV exposure predictions when used as a support tool for patients that require therapeutic drug monitoring, ii) be used as starting point to establish the pharmacokinetic-pharmacodynamic relationship between GCV exposure and CMV viral load, that in turn will allow refining the target exposure to be achieved and thus further optimize the dosage regimen to contribute to efficacy and safety in the target population.

Paracetamol (Acetaminophen) and Metabolites Population Pharmacokinetics Model in children and adults with Spinal Muscular Atrophy

MSc Qiaolin Zhao[1,2], MD Marie Mostue Naume[3,4], MD Sissel Sundell Haslund-Krog[5], Dr. Thomas Krag[3], Dr. Brenda C.M. de Winter[1,2], MD Karoline Lolk Revsbeck[3], Prof. John Vissing[3], Dr. Helle Holst[5], Dr. Morten Hylander Møller[6], Dr. Morten Morten[7], MD Christina Engel Høi-Hansen[4], Dr. Alfred Peter Born[4], Dr. Per Bo Andersen[4], MD Mette Cathrine Ørngreen[3,4], Brenda d Winter
[1]Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, Netherlands, [2]Rotterdam Clinical Pharmacometrics Group, Erasmus Univerity Medical Center, Rotterdam, Netherlands, [3]Copenhagen Neuromuscular Center, Department of Neurology, University Hospital of Copenhagen, Copenhagen, Denmark, [4]Department of Pediatric and Adolescent Medicine, University Hospital of Copenhagen, Copenhagen, Denmark, [5]Department of Clinical Pharmacology, Bispebjerg Hospital, Copenhagen, Denmark, [6]Department of Intensive Care, Copenhagen University Hospital, Copenhagen, Denmark, [7]Department of Clinical Genetics, Copenhagen University Hospital, Copenhagen, Denmark

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction

Spinal muscular atrophy (SMA) is neuromuscular disorder characterized by progressive muscular weakness and low skeletal muscle mass. Paracetamol is part of multimodal analgesia treatment in patients with SMA. Paracetamol is metabolized by the liver and the majority of its metabolites are glucuronide and sulfate. There is only a small portion of paracetamol excreted in urine as unchanged paracetamol or conjugated by cytochrome P450 CYP2E1 to a toxic metabolite, NAPQI. NAPQI is further conjugated by glutathione (GSH) to neutral metabolites and excreted in the urine as cysteine and mercapturic acid. We suspect that patients with SMA have a lower concentration of GSH, due to low muscle mass and malnutrition. Thus, children and adults with SMA may have increased risk of paracetamol toxicity. There is no published study investigating the pharmacokinetics (PK) of paracetamol in the SMA population. The aim of this study is to compare the differences in PK of plasma paracetamol, paracetamol-glucuronide, paracetamol-sulphate, paracetamol-oxidative metabolites, between SMA patients and healthy controls. We want to explore the separate contributions of the different metabolic pathways and assess the influence of physiologic covariates on paracetamol pharmacokinetics.

Materials and Methods

In this study, we collected 1764 plasma samples for paracetamol and its metabolites from 11 healthy adults, 6 adults with SMA and 6 children with SMA. Non-linear mixed-effects modeling (NONMEM) was used to develop a population pharmacokinetic model and perform a covariate analysis. Simulations were performed to investigate the impact of significant covariates on the exposure of paracetamol and its metabolites and compare the differences of the paracetamol and metabolites exposures in SMA patients and healthy controls.

Results

A one-compartment model with first-order absorption, lag time and allometric scaling best described the paracetamol and its metabolites in the population. The volume of distribution of SMA patients was 1.58-fold higher than healthy controls. Oxidative metabolites formation clearance is significantly different between SMA patients and healthy controls ($P<0.05$), and oxidative metabolites elimination clearance is only significantly different between SMA children and healthy controls. Myoglobin was a significant covariate on unchanged paracetamol clearance and bilirubin was a significant covariate on sulfate formation clearance and oxidative metabolites elimination clearance. Simulations from the model showed that glucuronide steady state exposure in SMA patients is lower than that in healthy controls ($P<0.05$), and higher myoglobin is accompanied by higher exposure in all compounds. We

can also see that half-life time of oxidative metabolites will increase when SMA patients have higher bilirubin.

Discussions and Conclusions

This is the first description of population PK of oral paracetamol intake in patients with SMA. We found that SMA patients have higher volume of distribution compared with healthy people, which indicates that SMA patients may have different body composition from healthy one. We can also see that oxidative metabolites formation and elimination clearance in SMA patients are lower than healthy ones due to they have less stocked glutathione to detoxify the intermediate metabolites.

The importance of model selection for a priori model informed precision dosing of vancomycin

PharmD PhD Sebastiaan Sassen[1,2,4], PharmD Bram Agema[1,2,3], Mr. Tolra Kocher[1], PharmD PhD Brenda de Winter[1,2,4], PharmD PhD Birgit Koch[1,2,4]
[1] Dept. of Clinical Pharmacy, Erasmus University Medical Center, Rotterdam, Netherlands, [2]Rotterdam Clinical Pharmacometrics Group, Rotterdam, The Netherlands, [3]Dept. of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands, [4]Center for Antimicrobial Treatment Optimization Rotterdam, Rotterdam, The Netherlands

Pharmacometrics, Møterom 5, september 25, 2023, 13:00 - 14:30

Objectives:
Vancomycin is a commonly used antibiotic for gram positive infections at the Intensive Care unit. However, in 2020 only 16% of the patients at the ICU in the Erasmus MC reached the intended target at the time of 20-25 mg/L at around 24 hours after the start of therapy. To improve target attainment, pharmacokinetic (PK) models can be used via dose individualization and optimization. This method has been shown to perform well, for example via Bayesian forecasting. Many pharmacokinetic models of vancomycin are available. Using the right PK model is of utmost importance, especially with a priori use of PK models where predictions are solely based using patients' characteristics to tailor the models. The aim of this study was to compare different methods of PK model selection to determine how to achieve the best a priori dose predictions for each individual patient to increase the number of patients within the target range at the start of the treatment.

Methods:
A retrospective analysis was performed in 100 patients at the Intensive Care Unit (n=90) and Orthopedics department (n=10) at Erasmus Medical Center in Rotterdam the Netherlands. All patients received vancomycin as a continuous infusion preceded by a bolus infusion. Patients on continuous renal replacement therapy and extracorporeal membrane oxygenation were excluded from the analysis. A total of 28 vancomycin PK models were replicated in Python (v. 3.7) and validated using NONMEM (v. 7.5). Model predictions were compared to the observed concentrations for each patient and each model. Dose simulations were performed for all patients and models to determine the optimal dose targeted at 22.5 mg/L at time of the first sampling (±24 hours). These results were used to test different dose selection methods. 1. Equally weighing of models; 2. Using the model with the lowest bias; 3. Excluding models based on quartiles of covariates where >75% of the patients deviated from the target; 4. Weighing of models based on model performance; 5. Model selection using decision trees (using R and rpart). The ratio between the administered dose and calculated dose was used to recalculate the observed concentration.

Results:
The average (range) of predicted over observed concentration for all models was 93.0% (56.3-135.7%) and the average standard error (range) was 38.3% (33.9-51.5%). The percentage of patients within the target range were 31.8%, 27.3%, 30.7%, 40.8% and 51.1% for respectively methods one through five. The method using decision trees performed best with an improvement from 31.8% to 51.1% of patients on target, followed by the weighing method which improved from 31.8% to 40.8%

Conclusion:
This study shows the importance of model selection for a priori model informed precision dosing. The dose prediction using all models did not perform better than no models. However, using model selection methods like performance-based model weighing and decision trees model

selection, the a priori dose prediction shows major improvements. This also endorses the importance of external validation and the importance of the choice of model(s) prior to clinical implementation.

Dual channel LC-MS/MS for quantification of four immunosuppressants in whole blood for therapeutic drug monitoring

Ms Tanja Zijp[1,2], Mr Kai Van Hateren[1], Mr Hiltjo Kuiper[1], Mr Erwin Jongedijk[1], prof.dr. Daan Touw[1,2]
[1]UMCG, Groningen, Netherlands, [2]University of Groningen, Groningen, The Netherlands

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Background: Liquid chromatography with tandem mass spectrometry (LC-MS/MS) is the golden standard for immunosuppressants analyses, where optimising throughput by parallel chromatography can reduce costs and turnaround time. We aimed to double our system throughput using a dual LC-MS/MS setup.

Methods: Two independent UPLC systems were hyphenated to one triple quadrupole MS, with staggered injections from one autosampler on alternating columns. The method simultaneously measured the analytes tacrolimus, sirolimus, everolimus and cyclosporin A in whole blood using isotope dilution, with a run time of 1.5 minutes. The dual LC-MS/MS results were compared to the standard single LC-MS/MS results in clinical samples over a period of one month.

Results: Net run-to-run time improved from 2.3 to 0.98 minutes per injection, where throughput increased from 26 to 61 injections per hour. Compared to the standard LC-MS/MS in 1101 clinical samples, there was excellent agreement for all four analytes as shown by Passing Bablok regression, with slopes of 0.98–1.02x and intercepts of -0.11–0.88. Minor bias was demonstrated between the systems with mean differences from -0.93 to 1.43% .

Conclusion: Throughput was doubled and idle MS time was reduced with good agreement to our previous system. The method is applied for clinical routine with frequent peak intensities of >180 injections per day.

Pharmacogenetic-guided Management of Fluoropyrimidines Dosing in DPYD Compound Heterozygosis

Dr. Giammarco Baiardi[1,2], MD Manuela Stella[1,2], MD Fabio Piras[1,2], Alessia Cafaro[2,3], MD Matteo Clavarezza[4], Stefania Casazza[5], Andrea Decensi[4], Prof. Francesca Mattioli[1,2]
[1]Clinical Pharmacology Unit, Ente Ospedaliero Ospedali Galliera, Genoa, Italy, [2]Department of Internal Medicine, Pharmacology & Toxicology Unit, University of Genoa, Genoa, Italy, [3]Chromatography and Mass Spectrometry Section, Central Laboratory of Analysis, IRCCS Istituto Giannina Gaslini, Genoa, Italy, [4]Medical Oncology Unit, Ente Ospedaliero Ospedali Galliera, Genoa, Italy, [5]Pathology Unit, Ente Ospedaliero Ospedali Galliera, Genoa, Italy

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction

Chemotherapic schemes in colorectal cancer (CRC) are still nowadays based on fluoropyrimidines (FPs). Individual variable expression of the limiting metabolizing enzyme dihydropyrimidine dehydrogenase (DPD) partly account for inter-patient variability in the FPs toxicity profile. The extremely polymorphic coding gene DPYD genetically determines DPD rate activity. Thus, pharmacogenetic-guided dosing of FPs-based regimens has been implemented in clinical practice to treat carriers of DPYD variants. Personalized dose adjustments are based on “DPYD activity score” (DPYD-AS) of different variants, which estimates the residual functionality of the DPD enzymatic system to translate the patients’ genotype into his most likely phenotypic response. Despite the Clinical Pharmacogenetics Implementation Consortium guideline implementation, a paucity of information exists regarding FPs dose adjustments in compound heterozygous variant carriers of DPYD polymorphisms.

We present a case of pharmacogenetic-guided fluoropyrimidines dosing of DPYD compound heterozygosis in a 48-year-old Caucasian man with a diagnosis of CRC pT3N0cM0, Grade 3, Vascular Invasion (VI), RAS wild type, BRAF wild type, Microsatellite Stable (MSS).

Materials and Methods

After acquisition of informed consent genomic DNA was isolated from peripheral blood using the MagCore Genomic DNA Whole Blood Kit (RB Bioscience Corp. CE IVD) and the mutational status analysis of the DPYD gene was performed by Real-Time Polymerase Chain Reaction using “EasyPGX DPYD Analysis Software” version 4.0.1. Allelic discrimination of the following single-nucleotide polymorphisms (SNPs) was performed: c.1905+1G>A (rs3918290; IVS14+1G>A; DPYD ∗2A), c.1129–5923C>G (rs75017182; IVS 10C>G/HapB3), c.1679T>G (rs55886062; p.I560S; DPYD ∗13), c.2846A>T (rs67376798; p.D949V) and c.2194G>A (rs1801160; p.V732I; DPYD ∗6).

Results

Genotypic assessment of DPD deficiency status that revealed a compound heterozygous alteration of the DPYD gene: c.1129–5923C>G (rs75017182; IVS 10C>G/HapB3) and c.2194G>A (rs1801160; p.V7321; DPYD ∗6).

Discussions and Conclusions

According to the disease stage (Stage II) patient should have received 8 cycles of CAP (capecitabine 2000 mg/m2/day for 14 days, every 3 weeks) as adjuvant therapy. Before starting CAP treatment as recommended clinical standard, DPYD polymorphisms genotypic status was assessed which revealed a compound heterozygous alteration of the DPYD (HapB3 and c.2194G>A). Thus, a clinical pharmacology consultation was requested to determine the most appropriate dose of CAP for the individualized treatment of the patient. Considering the most likely phenotypic expression of the assessed DPYD variants our patient was classified as a DPYD intermediate metabolizer (AS 1.5) and candidate to a 25% dose reduction of the starting dose from the first cycle of CAP. This choice was made with the intent of not compromising CAP efficacy and safety, since there was a residual risk of

unknown toxicity in the risk/benefit assessment, due to the simultaneous presence of a compound DPYD mutation previously never described. Treatment was discontinued at the 4th cycle for manifested low-grade toxicity. The combination of c.2194G>A to HapB3 could probably have anticipated Time-To-Toxicity due to an earlier over exposure to CAP. Oncological follow-up at 6-month confirmed no evidence of disease.
Pharmacogenetic-guided dosing of DPYD compound heterozygous variant carriers remains challenging and should be managed by a multidisciplinary team with a dose reduction aimed at balancing clinical efficacy with the safety of the treatment.

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Strengthening Chemical Risk Assessment through the Development of Adverse Outcome Pathways for Immunotoxicity Endpoints

Nicola Smith, Marcin Wojewodzic, Karine Bø, Hubert Dirven, Birgitte Lindeman[1]
[1]Norwegian Institute of Public Health, Oslo, Norway

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Society demands chemicals that are not toxic, bioaccumulative or persistent while at the same time using fewer animal experiments. To provide knowledge in support of these policies the EU has initiated the Partnership for the Assessments of Risks from Chemicals (PARC) as part of the Horizon Europe program. It is the first partnership of its kind to have EU agencies alongside national regulatory agencies addressing issues on the availability of chemical data and methods.

Two hundred universities, institutes and other organisations across Europe are partners in PARC. The objectives are to improve methods for exposure assessment in humans & the environment, develop New Approach Methodologies to assess the safety of chemicals and develop new and improved methods for risk assessment of chemicals for both humans & the environment.

One focus is on developing Adverse Outcome Pathways (AOPs) to facilitate chemical risk assessment by improving mechanistic understanding by linking a molecular initiating event with key events leading to an adverse outcome. NIPH is coordinating the development of AOPs for immunotoxicity focusing on immunosuppression

AOPs representing immunotoxicity endpoints are currently under-represented in AOP wiki (https://aopwiki.org/). There are three endorsed and one unendorsed AOPs identified for immunosuppression in the AOP-wiki (315, 154, 277 and 14, respectively). We have constructed a network based on these four AOPs. The network represents well-characterised modes-of-actions for different classes of immunosuppressive drugs. We used a SQL query to retrieve all the Key Events and Key Event relationships that were present in AOP-wiki. The network was further manually curated and visualised in Cytoscape.

An overview of the existing network of AOPs for immunosuppression and relevant descriptive statistics will be presented, in addition to the identified data gaps and prioritisation of PARC contributions to enhance the existing AOP network. The newly generated data and strengthened research networks in PARC are of direct relevance to regulatory work on a European- (ECHA and EFSA) and international level (WHO and OECD).

Etanercept (ETN) treatment of adenosine deaminase 2 deficiency (DADA2) for the prevention of ischemic events and the inflammatory biomarkers improvement: a case report.

Giorgia Babaglioni[1], Pharmacist Lorenzo Silva[1], Hospital Pharmacist Elena Festa[1], Hospital Pharmacist Daniela Paganotti[1], Phisician Francesca Crisafulli[2], Phisician Paolo Airò[2], Head Hospital Pharmacy Tullio Elia Testa[1], Head Rheumatology and Clinical Immunology Unit Franco Franceschini[2]
[1]ASST Spedali Civili of Brescia, Hospital Pharmacy, Brescia, Italy, [2]ASST Spedali Civili of Brescia, Rheumatology and Clinical Immunology Unit, Brescia, Italy

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DADA2 is an autoinflammatory disease caused by bi-allelic loss-of-function mutations in the ADA2 gene. Clinical features include systemic vasculitis that may manifest as early-onset ischemic events and/or hemorrhagic strokes, or as cutaneous or systemic polyarteritis nodosa (PAN); dysregulation of immune function and inflammatory markers, such as the C-reactive protein (CRP) and the serum amyloid A (SAA).

To evaluate the ETN treatment impact on the clinical management of a female patient with DADA2, by analyzing the vasculitic pattern, the ischemic events prevention and the inflammatory biomarkers improvement.

A 45-year-old woman was diagnosed with DADA2, genetically confirmed as a G47R homozygous variant. The patient was followed-up in a Italian rheumatological center for a previous diagnosis of PAN. ETN was then initiated at the dosage of 50 mg/w and the patient was followed-up every month for 14 months and evaluated for the disease activity, the CRP and SAA reduction, the incidence of new ischemic events and the rearrangement of the immunosuppressive therapy.

After the ETN beginning, the patient didn’t experience new ischemic events and iloprost was administered from 3-weekly to 4-weekly intervals for the treatment of the feet relapsing ischemic digital ulcers. Azathioprine dose was cut in half to 50 mg/die and the prednisone was reduced from 5.4 mg/die to 3.5 mg/die. Inflammatory acute phase proteins significantly decrease: in the previous year before ETN introduction, CRP reached a value of 33.8 mg/L (normal values < 5.0 mg/L) and the SAA was up to 22 mg/L (normal values < 8 mg/L), whereas in the next three months the CRP decreased to 5.7 mg/L and the SAA to 10 mg/L, till normalizing to 4.4 mg/L and 7 mg/L, respectively.

ETN allowed to prevent the occurrence of new ischemic events, to control vasculitic activity and inflammation markers as well. The therapy was well tolerated and allowed to reduce the cortisone and the concomitant immunosuppressive therapy, maintaining a good control of immune function, hematological values and systemic autoinflammatory manifestations. Furthermore, ETN had no impact on neutropenia and on the frequency of infectious occurrence.

Use of Dupilumab in the treatment of bullous pemphigoid: a case report.

Lorenzo Silva[1], Pharmacist Giorgia Babaglioni[1], Pharmacist Chiara Galuppi[1], Hospital Pharmacist Elena Festa[1], Head Hospital Pharmacist Tullio Elia Testa[1], Phisician Vincenzo Maione[2], Hospital Pharmacist Daniela Paganotti[1]
[1]ASST Spedali Civili of Brescia, Hospital Pharmacy, Brescia, Italy, [2]ASST Spedali Civili of Brescia, Dermatology, Brescia, Italy

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In 2021, a 75-year-old female patient was diagnosed with bullous pemphigoid, a chronic skin disorder, characterized by the presence of anti-BP180 antibodies. She was initially treated with systemic corticosteroids, as monotherapy and in combination with doxycycline, then discontinued due to the onset of dyspepsia. Dapsone was not recommended, considering the glucose-6-phosphate dehydrogenase (G6PD) deficiency, and the prednisone tapering led to progressive worsening of the clinical pattern. Dupilumab, a monoclonal antibody that inhibits the IL-4 and IL-13 activity and reduces uncontrolled TH2 lymphocyte differentiation and eosinophilic chemotaxis, was started in March 2022.

The objective of this case report is to highlight the clinical effect of subcutaneous dupilumab in a patient with bullous pemphigoid.

The off-label treatment was authorized upon presentation of the patient clinical report and supporting literature data. After providing informed written consent, subcutaneous dupilumab was started at the approved dose schedule for atopic dermatitis, that includes a 600-mg induction followed by 300 mg every two weeks. The estimated cost is about 10,000 euros/year. The patient was periodically followed-up in an out-patient setting.

After the introduction of dupilumab, the clinical pattern significantly improved. She had no skin blisters, and the itching was mild. However, even if anti-BP180 antibodies were 131 UR/ml, anti-BP230 antibodies were negative. In July, a relapse with urticarial lesions lead to a transient increase in prednisone dosage. After seven months, the patient didn’t experience skin lesions anymore, except for a residual chest lesion.

Dupilumab resulted to be effective in reducing the rash and the pruritus in seven months after the beginning of the treatment. Anti-BP230 antibodies were absent, while anti-BP180 antibodies persisted despite regression of symptoms. In a similar clinical case, the authors noted an instantaneous improvement from the first injection, and after three months the patient had resolution of the blisters with absence of anti-BP180 and BP230 antibodies. The patient is still followed-up in the dermatological center and the clinical course is steadily improving. Therefore, future studies will be conducted for confirming the efficacy of dupilumab in the treatment of this rare disease.

Pharmacokinetic Evaluation of Oral Viscous Budesonide in Pediatric Patients with Eosinophilic Esophagitis in Repaired Esophageal Atresia

PhD Raffaele Simeoli[1], Sara Cairoli[1], MD Marco Roversi[2], MD Renato Tambucci[3], MD Luigi Dall'Oglio[4], MD Carlo Dionisi Vici[1], MD Giuseppe Pontrelli[5], MD, PhD Oscar Della Pasqua[6], MD Paola De Angelis[3], Bianca Maria Goffredo[1]

[1]Division of Metabolic Diseases and Drug Biology, Bambino Gesù Children's Hospital IRCCS, Rome, Italy, [2]Residency School of Pediatrics, University of Rome Tor Vergata, Rome, Italy, [3]Digestive Endoscopy Unit, Bambino Gesù Children's Hospital IRCCS, Rome, Italy, [4]Digestive Endoscopy and Surgery Unit, Bambino Gesù Children's Hospital IRCCS, Rome, Italy, [5]Centre of Excellence for the development and implementation of medicines, vaccines, and medical devices for pediatric use, Bambino Gesù Children's Hospital IRCCS, Rome, Italy, [6]University College London, London, United Kingdom

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Introduction: Esophageal atresia (EA) is an uncommon condition that impacts approximately 1 in 3,000 infants. Individuals with EA experience complications, including gastroesophageal reflux disease (GERD) and anastomotic stricture (AS). Topical corticosteroids such as fluticasone and oral viscous budesonide (OVB) have been widely employed as off-label medication with demonstrated effectiveness and safety. Due to its limited systemic absorption, oral budesonide has a lower incidence of side effects compared to traditional glucocorticosteroids and is generally well-tolerated. Here, we report the application of a new LC-MS/MS method for pharmacokinetic analysis of OVB in EoE-EA children.

Materials and Methods: Budesonide was measured in plasma samples from pediatric patients (aged 3 to 18 years) with primary EA repair, who were diagnosed with EoE based on international criteria. In this study, a viscous formulation of budesonide at final concentration of 0.2 mg/ml was used. The LC-MS/MS method was validated according to EMA and FDA guidelines for bioanalytical methods validation. The area under the concentration-time curve from 0 to 12 hours after dose (AUC 0-12) was calculated using the trapezoidal linear rule from zero to the estimated concentration at 12 hours. Other PK parameters such as volume of distribution (Vd), plasma clearance (CL), drug half-life (t1/2) and trough plasma concentration (Cmin) were also calculated.

Results: During a 12-month screening period, the study included eight pediatric patients. Five patients in the 5-11.9 years group received 0.8 mg and three patients in the 12-18 years group received 1 mg of OVB every 12 hours. The concentration-time profile of OVB showed marked inter-individual variability. Three out of eight patients showed a positive dose-normalized 0-12 AUC. A high percentage of variability for Cmin and Cmax was observed, especially in the group of 5-11 years old patients treated with 0.8 mg of OVB twice daily (CV% Cmin DN= 69.60% and CV% Cmax DN= 120.33%). Overall, the budesonide peak occurred between 4 and 6 hours (mean= 4.85 hours) for the 5-11 years old group and between 2-3 hours (mean= 2.90 hours) for the 12-18 years old patients. Oral administration of viscous budesonide showed a dose proportionality, as Cmax was positively and significantly correlated with dose q12h (Spearman r=0.86, p=0.02). Monitoring of serum cortisol to test for adrenal suppression showed stable values for all patients throughout the study period.

Discussion and Conclusions: Our results show a high degree of inter-individual variability for the budesonide PK behaviour in our paediatric population. These differences are more evident at higher doses of budesonide. Following oral administration, part of viscous budesonide adheres to the oesophagus where topically acts, while another part of can absorbed into the systemic circulation. Considering the significant correlation between dose and Cmax, a higher amount of budesonide administered to 12-18 years old patients may be significantly proportional to the amount of drug

absorbed and measured in plasma. Further studies will be required to explore the PK properties of this viscous formulation on a larger cohort of pediatric patients.

Local experience on adalimumab and etanercept biosimilar drugs: safety and efficacy confirmation encourages rheumatologist biosimilar prescription.

Giorgia Babaglioni[1], Pharmacist Lorenzo Silva[1], Hospital Pharmacist Elena Festa[1], Hospital Pharmacist Daniela Paganotti[1], Head of Hospital Pharmacy Tullio Elia Testa[1], Head of Rheumatology and Clinical Immunology Unit Franco Franceschini[2]
[1]ASST Spedali Civili of Brescia, Hospital Pharmacy, Brescia, Italy, [2]ASST Spedali Civili of Brescia, Rheumatology and Clinical Immunology Unit, Brescia, Italy

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Biosimilars are biological medicines of rigorous pharmaceutical standard quality, that can provide benefits for patients in terms of safety, efficacy and quality, for healthcare systems as well in increasing treatment alternatives, access and cost competitiveness.

To evaluate the safety reports of subcutaneous biosimilars of adalimumab (ADA) and etanercept (ETN), the two biological pillars of rheumatology, by considering the patients therapies and safety signals collected in the local center.

A three years period analysis was considered after the introduction of the first biosimilar of ADA (2019) and ETN (2017): the safety reports occurred in this period were analyzed after being reported in the AIFA National Pharmacovigilance Network (RNF) database. Patients biological scheme assessments were defined by using an internal accounting system of provided drugs to outpatient and home regimen patients.

Etanercept was the first biosimilar subcutaneous anti-TNFα introduced in the rheumatological center: the switching practice was embraced for the 23.1% of patients (n=93) and the biosimilar prescription was adopted for the 26.2% naïve patients (n=105). The safety signal rate of ETN biosimilar/originator (0.6) was in favor of the biosimilar; 25% of the events were considered serious, with no difference between biosimilar and originator. Drug ineffectiveness was recorded both for originator and biosimilar with different rate (60% and 41.7% respectively), proving that the poor control of the disease should be independent by the drug formulation itself. The second generation biosimilars of adalimumab were introduced into the clinical practice much more incisively, thanks to the raising physician confidence acquired with ETN. The 37.7% of patients (n=283) in ADA originator were switched to biosimilar and the 47.7% (n=358) received biosimilars as first-line therapy. Although in this case there was a 38.5% of reports for perceived ineffectiveness of the biosimilars (n=13), they were all classified as not serious and signaling rate was still favoring the biosimilars (0.76).

From what emerges from the quantitative and qualitative analysis of the adverse reactions reported in the RNF, there are no specific safety concerns or clinically meaningful differences in the use of biosimilars. Indeed, doctors are increasingly supporting biosimilarity/interchangeability, combined with an appropriate level of communication with patients, that can enhance the biosimilars contribution to sustainability and patient therapy access.

Liposomal Amphotericin B consumption in intensive care units (ICUs) from 2018 to 2021.

Lorenzo Silva[1], Pharmacist Giorgia Babaglioni[1], Hospital pharmacist Elena Festa[1], Head hospital pharmacist Tullio Elia Testa[1], Hospital Pharmacist Daniela Paganotti[1]
[1]ASST Spedali Civili of Brescia, Hospital Pharmacy, Brescia, Italy

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

In the last few years Liposomal Amphotericin B (L-AmB) use has increased. COVID-19-associated pulmonary aspergillosis (CAPA) and Aspergillus tracheobronchitis (AT) represent severe Coronavirus disease complications. CAPA and AT are described to be frequently diagnosed in ICUs and nebulized L-AmB results to be effective, in mechanically ventilated COVID-19 patients, to prevent invasive pulmonary Aspergillosis.

Purpose of this retrospective study is to analyze L-AmB prescription prevalence from 2018 to 2021 in ICUs, investigating the consumption during the COVID-19 pandemic and the effect of the introduction of prophylaxis strategies.

The present single-centre experience in L-AmB consumption in ICUs has been performed by adopting the Defined Daily Dose (DDD) as benchmark. Results are expressed as number of DDDs/100 bed days (bd), to compare consumption of different years.

The DDD/100bd in 2018 and 2019 were comparable (2,18 and 2,28 respectively), indeed L-AmB use has significantly increased during 2020 and 2021. During 2020 consumption started to increase (3,51 DDD/100bd) up to tripled in 2021 (10.68 DDD/100bd). The monthly use began to increase from December 2020 (110,98 DDD/100bd) compared to a median 33,16 DDD/100bd in the previous months. The rising trend was registered for the first four months of 2021 reaching 227,78 DDD/100bd in April 2021 and then declined in the second part of the year (October 86.10 DDD/100bd - November 53.88 DDD/100bd). Indeed, the introduction in April 2021 of prophylaxis protocol with inhaled L-AmB, administered twice a week, combined with posaconazole (2), induces an approximately threefold reduction in L-AmB total consumption (277.78 DDD/100bd April 2021 vs 86.10 DDD/100bd August 2021). The total cost of this antifungal therapy (2020 vs 2021) increased 5.25 times, even if the vial/price remained unchanged.

Real data confirms that the L-AmB increased use is closely related to COVID-19 pandemic. Prolonged hospitalizations, use of systemic corticosteroids and severe or critical COVID-19 disease expose patients to Aspergillus infections. In conclusion, a L-AmB consumption reduction could be associated to the introduction of a prophylactic protocol together with the reduction of COVID-19-related hospitalizations and the increase in the vaccination campaign. The prophylactic protocol can be a useful approach to reduce sanitary costs, safeguarding patient health.

High-throughput UPLC-ESI-MS/MS method for the determination of Phosphatidylethanol (PEth) 16:0/18:1 in whole blood: the clinical application

Dr. Linda Sanderson[1]
[1]Karolinska Universitetssjukhuset, Huddinge, Sverige

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

High-throughput UPLC-ESI-MS/MS method for the determination of Phosphatidylethanol (PEth) 16:0/18:1 in whole blood: the clinical application
Linda Sanderson, Ying Lu
Droganalyslaboratoriet, Klinisk Farmakologi, Karolinska Universitetssjukhuset, Stockholm, Sweden
Linda.Sanderson@regionstockholm.se, Ying.Lu@regionstockholm.se

Abstract
Aim: Phosphatidylethanols (PEths), a series of abnormal phospholipids formed in the presence of ethanol and phospholipase D, are sensitive and specific biomarkers for alcohol consumption. Here, we report on the set-up, application and performance of a high-throughput UPLC-ESI-MS/MS method that was validated in clinical settings, for the determination of PEth 16:0/18:1 in whole blood.

Method: A simple and effective sample preparation was achieved by using isopropanol extraction on a 96-well plate in combination with a robotic liquid handling system. Briefly, venous whole blood (50 µL) and internal standard dissolved in isopropanol (400 µL) were added to the well plate, then subjected to vigorous shaking (1800 rpm for 5 minutes) and finally centrifuged (4500 rpm for 5 minutes). The supernatants were direct injected into a LC-MS/MS system (Waters Xevo -TQS µ) and PEth 16:0/18:1 was measured by using two MRM: 701.4->281.3 and 701.4->255.3. The LC separation employed a Kinetex 1.7µm XB C18 column (50 x2.1 mm, Phenomenex), a gradient of 3 minutes and mobile phases of 10 mM ammoniumbicarbonate-methanol-acetonitril.

Results: This method was validated on a calibration range of 0.025 -10 µM (with LOD 0.01 µM). Its long-term accuracy and precision are assured by both internal and external quality (EQUALIS) control programs. The method has been accredited for applications to clinical routines in our lab since 2017. Since then, the sample throughput has been increased (over 10% yearly). In 2022, more than 84,000 samples were analyzed, and 97% of these samples received results within 2 days from their arrivals in the laboratory.

Conclusion: We have established a routine method that combines an effective sample preparation procedure and a sensitive and robust LC-MS/MS determination of PEth 16:0/18:1 in whole blood. This method is successfully applied to high-throughput routine analyses in clinical settings, and its effectiveness and robustness has been proven by the long-term performance.

A NEW AND RAPID LC-MS/MS METHOD FOR DETERMINATION OF CYSTEAMINE PLASMA LEVELS IN CYSTINOSIS PEDIATRIC PATIENTS

Sara Cairoli[1], PhD Raffaele Simeoli[1], MD Marcella Greco[2], Alessia Vitale[1], Giacomo Antonetti[1], Alessandro Mancini[1], Bianca Maria Goffredo[1]
[1]Division of Metabolic Diseases and Drug Biology, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, [2]Division of Nephrology, Bambino Gesù Children's Hospital IRCCS, Rome, Italy

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction: Cystinosis is a rare lysosomal storage disorder caused by autosomal recessive mutations in the CTNS gene that encodes the cystine transporter cystinosin, which is expressed at the lysosomal membrane and mediates the efflux of cystine from the lysosome. Cystinosis is a systemic metabolic disorder that initially affects kidneys and, then, leads to multiorgan dysfunction. Cystine mainly accumulates in phagocytic cells—polymorphonuclear (PMN) leukocytes and monocytes—but not in lymphocytes. Cysteamine bitartrate is a cystine-depleting aminothiol agent approved in the United States and Europe for the treatment of nephropathic cystinosis in children and adults. Utility of performing TDM of Cysteamine is mainly based on the evaluation of therapy adherence. Here, we have developed and validate a LC-MS/MS method for determination of cysteamine in plasma samples.

Materials and Methods: This LC-MS/MS method was validated according to EMA and FDA guidelines for bioanalytical methods validation. Intra-day and inter-days precision and accuracy were evaluated as % coefficient of variation (CV) and mean % bias, respectively. Moreover, the stability of cysteamine was assessed as Quality Control (QC) samples stored at room temperature in the autosampler up to 14 days. An ultra-performance liquid chromatography (UPLC) 1290 Infinity II system coupled to a 6470 Mass Spectrometry system (Agilent Technologies) was used for cysteamine determination. Our validated method was applied to plasma samples of n= 4 cystinosis pediatric patients (mean age, 10 years). Samples were collected immediately before cysteamine oral assumption (PRE-DOSE) and 1 hour after (POST-DOSE). Patients were assuming an average daily dose of 1000 mg (range, 300-1900 mg/day).

Results: Our bioanalytical method was fully in agreement with EMA and FDA guidelines in terms of accuracy, precision, selectivity, specifity and carry-over. Both intra-day and inter-days accuracy and precision were ≤15%, as described by regulatory guidelines. Cysteamine stability was maintained at 90% of initial concentration (Time 0) after 24 hours from samples preparation and decreased to 50% following 48 hours of storage at room temperature in the autosampler. Calibration curve was linear over the range of 1.0-200 µM (R2=0.998, y=0.024*X + 0.014). Cysteamine plasma levels in PRE-DOSE samples were below the lower limit of quantification (LLOQ) (median, IQR) 0.21, 0.14-0.38 µM, whereas POST-DOSE samples reported a cysteamine median concentration of 2.22 µM (IQR, 1.75-3.50).

Discussion and Conclusions: Limited information is available on the pharmacokinetics and pharmacodynamics of cysteamine, with most studies involving only healthy adult subjects. Only few studies assessed the PK behaviour of cysteamine in pediatric patients affected by cystinosis. Here, we have developed and validate a new LC-MS/MS method for quantification of cysteamine in plasma samples. Our method is based on a quick and easy sample preparation and allows a rapid determination of cysteamine levels (run time= 5 minutes). This method has been successfully used for the quantification of cysteamine plasma levels in cystinosis pediatric patients and, therefore, could be a useful tool for both evaluation of therapy adherence and for future PK studies involving a higher number of pediatric subjects.

Population pharmacokinetics of Idarubicine and its active metabolite in acute myeloid leukaemia patients: Model development, evaluation and optimization

Dr Chadi Abbara[1], Dr Corentin Orvain[2], Dr Guillaume Drevin[1], Pr Norbert Ifrah[2], Pr Christian Recher[3], Dr Caroline Bazzoli[4], Ms Severine Ferec[1], Pr Philippe Guardiola[5], Pr Mathilde Hunault-Berger[2], Pr Marie Briet[1]

[1]Angers University Hospital - Pharmacology and Toxicology department, Angers, France, [2]Angers University Hospital - Blood Diseases department, Angers, France, [3]Cancer University Institut Oncolpole, Toulouse, France, [4]Grenoble Alpes University, Grenoble, France, [5]Angers University - UFR Santé, Angers, France

Oncology, Møterom 2, september 25, 2023, 13:00 - 14:30

Introduction:
Idarubicin pharmacokinetics (PK) is characterized by a large inter-individual variability (IIV) that may impact acute myeloid leukemia (AML) patient outcome. These observations raise questions about the optimal dose regimen for idarubicin that could be answered with a pharmacokinetic/pharmacodynamic (PK/PD) population study. To conduct such a study, a joint idarubicin/idarubicinol PK model following idarubicin administration in current schemes has to be established. To provide this model, we performed a prospective PK evaluation of idarubicin/idarubicinol in AML patients. The developed model was then assessed and optimized to define a population PK study design.
Methods:
27 patients were enrolled in the PK ancillary study of the BIG-1 trial, 6-8 samples were performed up to 24 hours after the first idarubicin dose administration (9 mg/m2/day, 30-minute IV). Idarubicin and idarubicinol plasma quantifications were performed using HPLC coupled with a fluorescence detector. Concentrations data were analysed using a nonlinear mixed effect model. The stochastic approximation expectation maximization algorithm implemented in the software MonolixSuite® 2021R2 (Lixoft®) was used to estimate the parameters. Structural models were built using user-defined ODE functions written in Mlxtran language. Model evaluation and optimization were conducted using the R function PFIM.
Results:
Idarubicin PK was best described by a three-compartment parent, two-compartment metabolite model, with a double first-order transformation of idarubicin to metabolite. Idarubicin elimination from the central compartment could not be identified since the value of the estimated elimination constant was extremely small and poorly estimated. Idarubicinol elimination was estimated through a grid approach and fixed in the final estimation step. Volumes of distribution of central compartments of both parent and metabolite were considered as equal. The error model that best fit the data was the proportional model for both substances (15% idarubicin, 12% idarubicinol). Structural model parameters were well estimated (estimation RSD% between 5.28% and 16.4%). The estimated IIV ranged between 25% and 54% confirming the high inter-individual variability of idarubicin/idarubicinol PK. A practical optimal population design has been derived from this model with five sampling time per subject (0.58, 1, 6, 10, 24) and this can be used for a future population PK/PD study.
Conclusion:
Our study provided a joint PK model of idarubicin and its metabolite in the current dosage that could be used for PK/PD population study.

Volumetric Absorptive Microsampling Technique as a Reliable Sampling Tool for Salivary Therapeutic Monitoring of Perampanel in Patients with Epilepsy

Dr. Michela Palmisani[1,2], Francesca Crema[1], Valentina De Giorgis[2], Costanza Varesio[2,3], Elena Tartara[2], Cinzia Fattore[2], Paola Rota[4,5], Giacinto Guercilena[6], Guido Fedele[7], Dr. Valentina Franco[1,2]
[1]Clinical and Experimental Pharmacology Unit, Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy, , , [2]IRCCS Mondino Foundation, Pavia, Italy. Member of ERN-Epicare, , Italy, [3]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, [4]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy, [5]Institute for Molecular and Translational Cardiology (IMTC), San Donato Milanese, , Italy, [6]B.S.N. srl R&D Laboratory, Castelleone, Italy, , , [7]Associazione Farmaceutici dell'Industria (AFI), Milan, Italy, ,
Alternative sampling strategies 2, Møterom 1, september 26, 2023, 13:00 - 14:30

Introduction
Volumetric absorptive microsampling (VAMS) is a novel minimally invasive microsampling technique used to obtain dried samples of microvolumes of different biological matrices for bioanalytical purposes including patient-friendly therapeutic drug monitoring (TDM) [1]. In this context it is well known that for many antiseizure medications, the concentration in saliva is identical to the concentration in plasma/serum, which allows the use of saliva instead of plasma/serum samples for monitoring purposes [2]. In a recent study the concentration of the new antiseizure medication perampanel in saliva was attested to be correlated with that in plasma [3].
Materials and Methods
The present study describes for the first time the development and validation of a new selective and sensitive analytical method for the determination of the antiseizure medication perampanel in saliva of patients with epilepsy collected by VAMS using liquid chromatography-tandem mass spectrometry (LC-MS/MS). 30 microliters of oral fluid were applied to VAMSs and dried for 60 minutes. VAMS tips were placed into clean tubes and after addition of the internal standard analytes were extracted with methanol. Samples were then incubated for 10 min at 50◦C, sonicated and centrifuged at 17000 g at 4°C. The supernatant was therefore evaporated at room temperature under a gentle stream of nitrogen, reconstituted with methanol and 20 µl were injected into the LC-MS/MS system. Separation and quantitation were achieved on a C18 column connected to a mass spectrometer.
Results
The developed VAMS-LC-MS/MS method exhibited good selectivity and correlation coefficient values for the calibration curves were >0.999 over the tested calibration range (0.5-300 ng/mL). The limit of quantitation was 0.5 ng/mL. Mean intra- and inter-day precision and accuracy were <12% and within 86-103% respectively. All analytes were stable in saliva VAMS samples stored at room temperature for 24 hours, after three freeze/thaw cycles and after 1 week at -20°C. Extraction recoveries were in the range of 81-99%. The applicability of the method to TDM was demonstrated by analysis of human saliva VAMS samples obtained from patients with epilepsy treated with perampanel.
Discussions and Conclusions
This is the first method using VAMS for the determination of an antiseizure medication in saliva and it enables the quantitation of perampanel in saliva with adequate accuracy, precision, recovery, specificity and sensitivity. The demonstrated stability of perampanel in VAMS is highly beneficial for sample shipment or storage at ambient temperature. The present VAMS-LC-MS/MS showed great potential for routine TDM use for its simplicity associated to the advantages related to the use of oral fluid as a matrix.

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CardioCarePack – personalized medicine system for TDM of cardiological drugs based on LC-MS/MS analysis of samples collected at home with VAMS.

PhD Rafał Szewczyk[1,2], PhD Adrianna Radulska[3], Msc Anna Lenartowicz[1], PhD Julia Mironenka[1], PhD Adrian Soboń[1,2], PhD Katarzyna Krupczyńska-Stopa[1,2], PhD Maciej Stopa[1,2], PhD Tomasz Borkowski[3], Msc Ewelina Marciniak[3], Prof. Leszek Kalinowski[3]
[1]Labexperts sp z o.o., Gdansk, Poland, [2]Bioanalytic sp z o.o., Gdansk, Poland, [3]Medical University of Gdansk, Gdansk, Poland

Alternative sampling strategies 2, Møterom 1, september 26, 2023, 13:00 - 14:30

Introduction

Cardiac arrhythmia affects approximately 12.6% of people over the age of 65. Ventricular arrhythmias are considered as responsible for 75% to 80% of sudden cardiac deaths. Drug therapy monitoring (TDM) in Anti-Arrhythmic Drugs (AAD) is essential for patient management when their have narrow therapeutic range, their use is associated with several serious adverse drug reactions, has a long, multiphasic elimination of up to several dozen days or formation of active metabolites with the action distinct form the parent drug. Developed assay named “CardioCarePack” is based on the use of capillary blood collected at home by a patient with volumetric absorptive microsampling (VAMS), quantitative analysis of selected drugs and their metabolites and a telemedical system that integrates all data between a doctor, patient and laboratory supporting the therapy process.

Materials and Methods

The project involved more than 300 patients who had been monitored for 2 years during regular pharmacological therapy. Patients were divided into 4 groups with the main anti-arrhythmic drug (Amiodaron, Propafenon, Sotalol and Digoxin), where additional ADD could also be administered. Every half a year during a visit in medical facility venous blood and capillary blood acquired by VAMS on 20 µl microsampling device (MITRA®) were collected. Between the visits patients were collecting samples by VAMS themselves at home. Samples were subjected to LC-MS/MS analysis QTRAP mass spectrometers (SCIEX). The LC-MS/MS method developed for 17 compounds covers therapeutic range of the tested compounds: 0.25 - 25 ng/ml (Digoxin and Nebivolol) 2.5 - 250 ng/ml (Metoprolol, Bisoprolol, Propafenone, Carvedilol, Perindopril, Ramipril, Spironolactone, Zofenopril and 25 - 2500 ng/ml (Sotalol, Desethylamiodarone, Eplerenone, Amiodarone, 5-hydroxypropafenone).

Results

On the basis of samples collected during 4 visits in medical facility a correlation between drugs concentration in venous blood (serum) and capillary blood (MITRA®) (S/M) was calculated. For some compounds S/M ratio was close to 1 (ex. Sotalol - 0.95, %CV - 5.12%, Nebivolol - 1.03, %CV - 3.17%) or moderately to more than 2-fold different (ex. Digoxin - 0.69, %CV - 1.46%, Ramipril - 1.18, %CV - 11.1, Perindopril - 1.86, %CV - 4.73%, Amiodarone - 2.17, %CV - 10.78). The correlation factors are statistically significant ($p < 0.05$) and can be used for accurate concentration estimation in venous blood. Statistical analysis has also showed excellent correlation between two laboratories with the analysis on QTRAP 4500, 5500+, 6500+ mass spectrometers (Spearman correlations above $R = 0.96$). Processed data are placed in a server-based telemedical system where history, doses, therapeutic index flagging, cardiograms and other diagnostic results and data are available for patient, doctor and laboratory staff, respectively.

Discussion and Conclusions

The SARS-CoV-2 pandemic has forced changes in healthcare management because of the patients isolation and difficult access to the doctor. CardioCarePack helps in doctor's supervision over the patient's condition on the basis of collected within the software data and fits in with modern trends of home-based sample collection and personalized medicine.

The project was co-financed by The National Centre for Research and Development and European Regional Develoment Fund. Grant no: POIR.01.01.01-00-1196/19

Development of a CZE-MS/MS method with on-line sample preconcentration for sensitive analysis of two main psychoactive indole alkaloids of Mitragyna speciosa in urine samples

PharmDr. Andrea Horniaková[1,2], prof. RNDr. PhD. Peter Mikuš[1,2], Assoc. Prof. PharmDr. PhD. Juraj Piešťanský[2,3]
[1]Department of Pharmaceutical Analysis and Nuclear Pharmacy, Faculty of Pharmacy, Comenius University in Bratislava, Bratislava, Slovakia, [2]Toxicological and Antidoping Center, Faculty of Pharmacy, Comenius University in Bratislava, Bratislava, Slovakia, [3]Department of Galenic Pharmacy, Faculty of Pharmacy, Comenius University in Bratislava, Bratislava, Slovakia

Toxicology -clinical and environmental, Sal C, september 26, 2023, 13:00 - 14:30

Introduction

New psychoactive substances (NPS) represent a novel heterogenous group of drugs of abuse. A very actual problem is the lack of the legislative regulation of NPS. It is due to their rising number on the illegal market. Kratom (Mitragyna speciosa Korth.) also belongs to NPS. Main psychoactive compounds of kratom, i.e. mitragynine and its metabolite 7-hydroxymitragynine, are characterized by their dose-dependent effect. For identifying mitragynine and its metabolite in complex matrices, liquid chromatography is a gold standard, but alternative separation methods such as capillary zone electrophoresis (CZE) are on the rise. CZE represents green analytical method characterised by high separation efficiency, low costs and minimal sample and chemicals consumption. Our goal is to develop a method based on CZE hyphenated with mass spectrometry (MS) detection for determination of mitragynine and 7-hydroxymitragynine in urine model samples using online sample preconcentration strategy.

Materials and Methods

The electrophoretic experiments were performed with an Agilent 7100 capillary electrophoresis system (Agilent Technologies, Santa Clara, CA) coupled with an Agilent 6410 Series Triple Quadrupole tandem mass spectrometer (Agilent Technologies) in positive electrospray ionization mode (ESI+). The separation was carried out in bare fused silica capillary with 50 µm ID, 300 µm OD, and total length 90 cm (MicroSolv Technology Corporation, Eatontown, NJ). The samples were injected hydrodynamically at 50 mbar for 10 s. Experiments were conducted in positive polarity, applying voltage of 20 kV during electrophoretic separations.

Results

During the optimization procedure precursor and product ions for mitragynine (MIT) and 7-hydroxymitragynine (7-OH-MIT) were identified. For further quantitative purposes the following precursor ion-product ion m/z transitions were selected: a) MIT: 399.3 → 174.1; b) 7-OH-MIT: 415.3 → 190.1. The ESI and MS conditions, such as sheath flow composition and flow rate, capillary voltage, fragmentor voltage, nebulizing gas pressure, drying gas temperature, or drying gas flow rate were optimized for both studied analytes. The separation was performed in a background electrolyte composed of 100 mM formic acid (pH 2.4).
The linearity of the developed method was performed with the use of calibration standard in the concentration range 10 – 150 ng/mL and 20 – 150 ng/mL for MIT and 7-OH-MIT, respectively. On-line sample preconcentration based on dynamic pH junction (DPJ) led to achievement of LOD values at 0.5 ng/mL and 2 ng/mL concentration level for MIT and 7-OH-MIT, respectively. Acceptable RSD and RE values were obtained when assessing accuracy and precision in according to FDA guidelines for bioanalytical method validation. Finally, the newly developed CZE-MS/MS method was applied to determine MIT and 7-OH-MIT in spiked model urine samples successfully.

Discussion and Conclusions

A separation method based on an on-line combination of CZE-MS/MS was developed for determination of indole alkaloids mitragynine and 7-hydroxymitragynine in model urine samples. In addition, online sample stacking was applied. The developed method was validated according to the FDA guidelines for biomedical methods. This work was supported by research grant UK/62/2023.

Development and clinical application of a CZE-MS/MS method for the analysis of colistin in plasma samples

PharmDr. Ivana Čižmárová[1,2], prof. RNDr. PhD. Peter Mikuš[1,2], Assoc. prof. PharmDr. PhD. Juraj Piešťnaský[2,3]
[1]Department of Pharmaceutical Analysis and Nuclear Pharmacy, Faculty of Pharmacy, Comenius University in Bratislava, Bratislava, Slovakia, [2]Toxicological and Antidoping Center, Faculty of Pharmacy, Comenius University in Bratislava, Bratislava, Slovakia, [3]Department of Galenic Pharmacy, Faculty of Pharmacy, Comenius University in Bratislava, Bratislava, Slovakia

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction

Colistin is a peptide antibiotic whose use has been restricted due to its neurotoxicity and nephrotoxicity. The rise of multidrug-resistant bacterial strains marked the rebirth of colistin, which is currently used as the antibiotic of last choice in critically ill patients for the treatment of infections caused by Gram-negative bacteria. Colistin is a heterogeneous mixture of lipopeptides with variable composition. The content of the major antibacterially active substances colistin A (CST A) and colistin B (CST B) varies not only from manufacturer to manufacturer but also in different batches of the same manufacturer. In clinical environment, TDM of colistin is recommended because of its variable PK and narow therapeutic window. Here, we developed and applied for the first time a simple capillary electrophoresis–tandem mass spectrometry method for determination of peptide antibiotic colistin in human plasma samples. This method combines the high separation efficiency of CE and the high sensitivity and selectivity of MS. This combination creates a greener and more economical alternative to the routinely used LC-MS methods in clinical laboratories.

Materials and Methods

The electrophoretic experiments were performed with an Agilent 7100 capillary electrophoresis system (Agilent Technologies, Santa Clara, CA) coupled with an Agilent 6410 Series Triple Quadrupole tandem mass spectrometer (Agilent Technologies). The separation was carried out in a bare fused silica capillary with 50 µm ID, and 300 µm OD, and the total length of the capillary was 90 cm (MicroSolv Technology Corporation, Eatontown, NJ). The samples were injected hydrodynamically at 50 mbar for 20 s. 50 mM formic acid was chosen as the background electrolyte. Experiments were conducted in positive polarity, applying a voltage of 25 kV during electrophoretic separations. For the sample pretreatment only a simple precipitation of proteins with acetonitrile was needed. 30 µL of plasma was sufficient for the analysis.

Results

For TDM purposes, plasma CST concentration is calculated as the sum of CST A and CST B. The CE-MS method was validated for each substance separately with the same method set up. We achieved LOD and LLOQ values at ng/mL levels for both investigated substances. The full validated method was finally applied to 14 plasma samples of a critically ill patient. During the time window of colistin administration, we measured the mean plasma concentration in patient samples at 1.69 µg/mL concentration level.

Discussion and Conclusions

By applying the developed method to real clinical samples, we confirmed the functionality of the method. Moreover, it was also observed that concomitant medication administered to the patient did not cause any interferences in the analyses. We confirmed the potential of the method to be used in TDM of colistin.

This work was supported by research grant FAFUK/20/2023.

Development of a rapid LC-MS/MS method for Ceftaroline and its metabolite measurement in biological fluids.

Bruno Casetta[1], Dr Michele Senatore[2], Dr Antonio Martini[3], Dr Sara Marzatico[1], Dr Gianluca Gazzaniga[4], Dr Sergio Finazzi[3], Prof Adriana Pani[5], Prof Frasncesco Scaglione[5]
[1]BSN, Castelleone, Italy, [2]Chemical-Clinical Analyses, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy, [3]Biochemistry Lab., ASST Ovest Milanese, Legnano Hospital, Legnano, Italy, [4]School of Clinical Pharmacology and Toxicology, Università degli Studi, Milano, Italy, [5]Department of Oncology and Hemato-Oncology, Università degli Studi , Milano, Italy, [6]Chemical-Clinical and Microbiological Analyses, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction
Few studies have been published so far on the pharmacokinetics of the antimicrobial drug ceftaroline. In order to support some preliminary research studies in hospital premises, a rapid protocol has been developed for the measurement in blood, plasma, serum and urine of both the drug itself and its main metabolite (M-1). Although no biological activity is reported for this metabolite, its measurement can make a significant contribution to the interpretation of the drug's ADME cycle.

Materials and methods
Pilot tests have been performed on anonymized biological samples. After a protein precipitation step, the extract was injected on an LC-MS/MS system preceded by a chromatographic process capable of clearly distinguishing the metabolite from the drug.
The calibration curve for the drug was obtained from the drug powder and by spiking a blank plasma. For the calibration of the metabolite, in the absence of an available external standard, a particular strategy has been adopted which exploits the rapid degradation, either chemical or/and enzymatic, of the precursor drug.

Results
With the injection of 0.1 µL of extract, representing 0.033 µL of biological liquid, a limit of quantitation of 64 ng/mL is reached with a linearity spanning up to 40 µg/mL of the active drug and the instrumental measurement lasts 7 minutes (injection-to-injection).
For the metabolite, since the strategy used cannot guarantee the same measurement accuracy as the drug itself, the provided values are in any case very consistent to express the relative variations in the various biological samples.

Discussion and conclusion
The first studies have confirmed robustness, sensitivity, and speed of the protocol.
The aforementioned prompt degradation of the drug when placed in a liquid medium, which enabled the strategy to provide a reference for the quantification of the M-1 metabolite, has also confirmed how critical are timing and conditions of collection and storage of the biological specimen, and as well the speed in the execution of the measurement protocol.

Voriconazole therapeutic drug monitoring – external evaluation of pharmacokinetic model predictive performance

PharmDr. Eliška Maraczek Marková[1,2], PharmDr. Bc. PhD. Kateřina Horská[1,2], PharmDr. MBA Šárka Kozáková[1,3]
[1]Department of Clinical Pharmacy, Hospital Pharmacy, The University Hospital Brno, Brno, Czech Republic, [2]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Masaryk University, Brno, Czech Republic, [3]Department of Pharmacology, Faculty of Medicine, Masaryk University, Brno, Czech Republic

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

1. Introduction

Voriconazole is a second-generation triazole antifungal primarily used as a first-line treatment for Aspergillus spp. infections with wide inter- and intra- individual variability in pharmacokinetics. Therefore, TDM of voriconazole should be performed for most patients. To perform TDM in routine clinical practice and fully use its potential, precise and possibly subpopulation-specific pharmacokinetic models are required. Our study aims to assess the interindividual variability in voriconazole pharmacokinetics, target specific subpopulations of patients, and identify relevant comorbidities affecting apparent pharmacokinetic variability. Correspondingly, we aim to evaluate the predictive performance and reliability of the currently available pharmacokinetic model.

2. Materials and Methods

An external evaluation study cohort of 30 patients treated with voriconazole at University Hospital Brno. Data collected: measured voriconazole plasma levels, descriptive patient data, and basic biochemical and hematological parameters. Data were analyzed in the context of the target reference range, and the prediction error of the voriconazole pharmacokinetic model (voriconazole_C2_v2 model, MWPharm Online, Mediware a.s., version 1.7.6.0) was assessed. Prediction error was calculated as the difference between the predicted voriconazole level and the corresponding measured level.

3. Results

From all of the voriconazole levels measured at a steady state (n=72), only 63% are within the target therapeutic range for voriconazole treatment (1,0 – 5,5 mg/l), 26% are subtherapeutic, 11% are supratherapeutic. Mean measured voriconazole level 2,75 mg/l (SD=5,98); voriconazole dosing is either on-label or higher. Nearly one-half of measurements are subtherapeutic when a minimal target through concentration is considered 2 mg/l, as recommended due to rising Aspergillus spp. resistance. On-label voriconazole dosing frequently leads to subtherapeutic measured levels (below 1,0 mg/l) – in nearly 40% of the cases. Based on our clinical experiences and preliminary results, the inter (and even intra-)- individual variability in voriconazole pharmacokinetics is high. The effect of the C-reactive protein and body weight on voriconazole levels, recently discussed in the literature, is also assessed in our study. These variables show a considerable impact on voriconazole levels; supratherapeutic voriconazole levels are most frequently measured in patients with a high level of CRP (> 100 mg/l). Moreover, we calculate the prediction error of the population pharmacokinetic model. In the initial phase, the mean prediction error is 3,43 mg/l (SD=2,13); minimal and maximal differences are 0,22 and 7,59 mg/l, respectively. After fitting, the mean predictive error is lower -2,81 mg/l (SD=1,57). More than half of the predictions are considerably higher than measured levels for both primary and fitted predictions.

4. Discussions and Conclusions

These preliminary data confidently demonstrate the importance of routine voriconazole TDM and support the urgent need for precise and subpopulation-specific pharmacokinetic models for higher

clinical utility of voriconazole TDM. Besides that, the data raise the question of standard dosing recommendation adjustments.

Utility of therapeutic drug monitoring to evaluate kinetics of antibiotics in pediatric patients affected by septic shock and subjected to continuous kidney replacement therapy and cytosorb hemoperfusion

Bianca Maria Goffredo[1], MD Marco Marano[2], MD Isabella Guzzo[3], MD Andrea Cappoli[3], MD Raffaella Labbadia[3], Sara Cairoli[1], Chiara Rossi[1], PhD Raffaele Simeoli[1], MD Gabriella Bottari[2]
[1]Division of Metabolic Diseases and Drug Biology, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, [2]Pediatric Intensive Care Unit, Department of Emergency, Acceptance and General Pediatrics, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, [3]Department of Pediatrics, Division of Nephrology and Dialysis, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

Anti-infectives 1 - antibiotics and antifungals, Sal B, september 25, 2023, 13:00 - 14:30

Introduction: Septic shock and multiple organ failure remain a leading cause of pediatric mortality worldwide. Cytosorb (CytoSorbents Corporation, New Jersey, USA) is a hemoadsorption cartridge containing hemocompatible porous polymeric beads. Combination of Cytosorb (CS) with the hemofilter (HF) in Continuous Kidney Replacement Therapy (CKRT) is used to treat acute kidney injury (AKI) in children with septic shock. Critically ill pediatric patients, especially those under extracorporeal therapies are characterized by complex pharmacokinetic (PK) profiles. In particular, blood purification techniques could also increase clearance (CL) of antibacterial agents leading to sub-therapeutic drug levels and, indeed, to the risk of therapeutic failures. Here, we report the application of therapeutic drug monitoring (TDM) to evaluate the contribute of hemoadsorption on the elimination rate of different antibiotics.

Materials and Methods: We retrospectively reviewed n=7 cases of pediatric septic shock (age between 1 month and 17 years) who received hemoperfusion with CS while subjected to CKRT. For each patient, levels of meropenem, ceftazidime, amikacin and levofloxacin were analyzed in blood samples collected at the following points of extracorporeal circuit: before and after HF, after CS, and in the waste bag. Ultra-high-performance liquid chromatography (UHPLC) methods were validated according to EMA and FDA guidelines to measure antibiotics' concentrations. The UHPLC apparatus used for determination of meropenem, ceftazidime and levofloxacin levels was an Agilent 1290 Infinity II system (Agilent Technologies). Meropenem and ceftazidime were measured by using a CE/IVD validated HPLC kit (Antibiotics in serum/plasma) provided by Chromsystems (Chromsystems Instruments & Chemicals GmbH). Levofloxacin levels were determined by using a previously validated and published UHPLC method [2]. An ultra-performance liquid chromatography (UPLC) 1290 Infinity II system coupled to a 6470 Mass Spectrometry system (Agilent Technologies) was used for amikacin determination.

Results: Based on antibiotic concentrations measured following method validation, both HF clearance (HF-CL) and Cytosorb clearance (CS-CL) were calculated in order to evaluate the individual contribute of both extracorporeal techniques on total antimicrobial clearance. For meropenem the higher contribute to the total clearance was provided by hemofilter (67%) compared to cytosorb (33%). Similarly, for ceftazidime the hemofilter contribute to drug clearance was higher (87%) than cytosorb (12%). Same values were reported for amikacin where HF significantly affected total clearance compared to CS (87% vs 12%). Finally, for levofloxacin the contribute of HF to clearance was 61% against 38% provided by CS.

Discussion and conclusions: TDM is useful to monitor and characterize antibiotic levels in pediatric patients subjected to hemoperfusion associated to CKRT. In fact, pharmacological treatments, including antimicrobial therapies, requires special PK considerations when administered in critical clinical settings such as CKRT and extracorporeal membrane oxygenation (ECMO). In this context, TDM as part of a multidisciplinary teamwork allows dose adjustments and facilitates safe and effective treatments. By using TDM data, we are able to observe that Cytosorb hemoperfusion seems

to have a negligible impact on meropenem, ceftazidime, amikacin and levofloxacin clearance in comparison to CKRT. However, more evidences will be needed to confirm our data.

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Pharmacokinetics-Pharmacodynamic study of subcutaneous infusion of daptomycin in healthy volunteers

Dr Marie-Clémence Verdier[1], Dr Charles Maurille[2], Dr Christian Creveuil[3], Dr Aurélie Baldolli[2], Pr Renaud Verdon[2,4], Bénédicte Franck[1], Emmanuelle Comets[1]
[1]Univ Rennes, CHU Rennes, Department of Pharmacology, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, F-35000 Rennes, , France, [2]Normandie Univ, UNICAEN, CHU de Caen Normandie, Department of Infectious Diseases, , , France, [3]Normandie Univ, UNICAEN, CHU de Caen Normandie, Department of Biostatistics and Clinical Research, 14000 Caen , , France, [4]INSERM U1311 DynaMicURe, Normandie University, UNICAEN, UNIROUEN, 14000 Caen , , France

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Background
Daptomycin is one of the most widely used antibiotics for the treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections. Its intravenous (IV) route of administration can be a limiting factor for its administration. The objective of this study was to assess the safety and the pharmacokinetics of daptomycin administered by subcutaneous (SC) route.

Methods
A single-blind, cross-over study was conducted in healthy volunteers over 18 years old. Each subject received daptomycin (10 mg/kg) alternately IV and SC. Daptomycin concentrations were measured at ten times after administration for pharmacokinetics (PK) study. A population-PK model was elaborated (Monolix2021R1) and Monte-Carlo simulations were used to evaluate the probability of target attainment (PTA).

Results
A total of 12 subjects (30.9±24.4 years, 75% males) were included. Local effects were more frequent in SC daptomycin group compared to SC placebo group (25 versus 13, p=0.016), but resolved quickly. No severe adverse reaction have been reported for either the IV or SC route. Main AEs were pain, erythema and oedema, more frequent in SC daptomycin group compared to SC placebo group (25 versus 13, p=0.016), but resolved quickly and spontaneously within 24 hours post injection. No cutaneous necrosis was reported. In terms of PK, a two-compartment model with a first-order absorption for SC route best described PK data. The only covariate retained was weight. The goodness-of-fit is very satisfactory and the estimation of the parameters is accurate (rse<15%). Compared to IV route, SC route produced a lower peak of concentration (132.2±16 µg/mL for IV versus 57.3±8.6 µg/mL for SC (p<0.001)). AUC0-24h of SC infusion was significantly lower than IV infusion (937.3±102.5 vs 1056.3±123.5µg/mL*h, p=0.005). For the most common 10 mg/kg/d dosage, 3% of patients had a risk of overcoming the toxic minimum concentration (24.3 mg/L) and 100% of patients achieved the target AUC of 666µg/mL*h defined for MRSA.

Conclusions
SC infusion of daptomycin was shown to be safe after one injection. These results suggest that the SC route could be a potential alternative to the IV route for daptomycin infusion but requires further clinical studies to assess the safety of repetead administrations and clinical efficacy.

Simultaneous HPLC-DAD determination of flecainide, amiodarone and desethylamiodarone based on internal and external standardization in cardiac pediatric patients with arrhythmia

MSc Agnieszka Czajkowska[1], MSc Marta Górska[1], MSc MPharm Arkadiusz Kocur[1,2]
[1]Pharmacokinetics Laboratory, Children's Memorial Health Institute, Warsaw, Poland, [2]Department of Drug Chemistry, Medical University of Warsaw , Warsaw, Poland

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Amiodarone (AM), a class III antiarrhythmic, is one of the most frequently used cardiological drug in pediatric population. AM is useful in management of both atrial and ventricular tachyarrhythmia's. Clinical effects of action include prolongation of myocardial cell action potential duration and recovery. This drug is metabolized to desethylamiodarone (DEA), which pharmacological activity is unknown, but would be correlated with drug toxicity. Flecainide is another drug used in patients suffering with arrhythmia, also in pediatric population, to prevent tachycardia. This agent is rated to class Ic of Vaughan-Williams classification. Pharmacokinetic depends on patient's age, genetic profile and other xenobiotics. Despite to that facts, therapeutic drug monitoring (TDM) of FL and AM as well as DEA is greatly needed.

High-performance liquid-chromatography method for simultaneous determination of AM, FL and DEA has been fully developed and validated. Additionally, two different URIS (structurally unrelated internal standard) were tested during validation, namely: promazine (PRO), imipramine (IMI) and mitotane (MIT). Only in case of first two compounds, retention time in relations to analytes were < 200% of set time. As analytical column has been chosen Poroshell 120-C_8 (4.60 x 150 mm, 2.7 µm) with guarded pre-column (2.1 x 5 mm, 2.7 µm). The Agilent Infinity II 1290 HPLC equipment with DAD detection was used for chromatographic determination of compounds. The flow rate was set at 1 mL/min, while detection wavelengths were: 242 and 261 nm for AM, DEA and FL respectively. As mobile phase was used gradient mixture of water buffered with phosphates, acetonitrile and methanol. Analytes from sample were isolated using LLE (liquid-liquid extraction) with hexane, and subsequently evaporated under nitrogen to dryness. After that residue was solved in mobile phase and 20 µL of that were injected into HPLC-DAD.

The method has been validated according to EMA guidelines about Bioanalytical Methods Validation. Calibration range for AM was 0 – 2000 ng/mL, while for DEA and FL 0 – 800 ng/mL. During validation, the parameters were evaluated such as: linearity, accuracy, precision, matrix effect, stability under different conditions. All parameters fulfilled EMA acceptance criteria. Working solutions as well as samples were stable during storage in autosampler at 4°C during minimum one week, at RT during three days, whereas during freezing at -20°C minimum one month.

Validation based on promazine and imipramine characterized by equal results accuracy. Additionally, based after experiments, the external standardization gives worst results in comparison to standardization with IS. Utility of validated method were confirmed using serum samples from patients treated with AM and/or FL. Measured concentrations were within calibration range.

Ocrelizumab concentration and antidrug antibodies are associated with B-cell count in multiple sclerosis

Nadine Wilhelmina Maria Commandeur[1], Expert Scientist Karien Bloem[1], MD, PhD Alyssa A Toorop[2], Neurologist Zoé L E van Kempen[2], Laura Hoogenboom[2], Merve Kocyigit[2], Anne Wijnants[1], Birgit I Lissenberg-Witte[3], Eva M M Strijbis[2], Bernard M J Uitdehaag[2], Theo Rispens[1], Joep Killestein[2], Floris Loeff[1], Annick de Vries[1]
[1]Sanquin Diagnostic Services, Amsterdam, Netherlands, [2]Department of Neurology, MS Center Amsterdam, Amsterdam UMC Location VUMC, Amsterdam, Netherlands, [3]Department of Epidemiology and Data Science, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction:
Biologics are the fastest growing class of drugs. Ample evidence is presented that the fixed dose paradigm for biologics results in sub-optimal treatment for a substantial portion of patients. Nonetheless, on-label dosing remains common practice. Therapeutic drug monitoring (TDM) is vitally important to establish the therapeutic window and to optimise therapy, preventing under- and overdosing.

Ocrelizumab is a humanized B-cell depleting monoclonal antibody approved for the treatment of adults with relapsing multiple sclerosis and primary progressive multiple sclerosis. On standard ocrelizumab interval, no circulating B-cells are detected upon re-dosing in most patients suggesting overtreatment. With B-cell-guided dosing patients receive their next dose only when B-cell repopulation already occurs. Prediction of B-cell repopulation using ocrelizumab level could aid in personalising treatment regimes. The objective of this study was to develop assays to measure ocrelizumab serum level and antidrug antibodies (ADAs). Finally, the association between ocrelizumab level, ADAs and B-cell count was evaluated.

Methods and materials:
An enzyme-linked immunosorbent assay (ELISA) and a radioimmunoassay (RIA) were developed and validated to measure ocrelizumab level and ADA. The ELISA captures ocrelizumab from serum using anti-idiotype antibodies specific for ocrelizumab and biotinylated anti-ocrelizumab conjugate to subsequently detect bound ocrelizumab. The RIA uses multispecies fc coated Sepharose beads to capture total IgG, with subsequent detection of specific ADA using biotinylated ocrelizumab and radioiodine labelled streptavidin. These assays were used to analyse 452 blood samples collected 1-67 weeks after ocrelizumab infusion from seventy-two patients.

Results:
Because ocrelizumab is dosed intravenously with a large interval the concentration range of ocrelizumab present in the serum is large. Subsequently, the assay was set-up in such a way that a very wide range of concentrations could be accurately measured. This resulted in a highly sensitive ELISA with a broad range; lower limit of quantitation of 0.0025 µg/mL and an upper limit of quantification of 1200 µg/mL. Average bias at six spike levels was 12% and the average intra and inter assay precision were 8% and 10%, respectively. The cut-off for ADA positivity in the RIA was 87.5 arbitrary units per mL. Ocrelizumab was detectable up to 53.3 weeks after the last infusion and ranged between <0.0025 and 204 µg/mL after 1-67 weeks. Ocrelizumab concentration was negatively associated with B-cell count. Using <10 CD19 B-cells/µL as cut-off, ocrelizumab levels > 0.06 µg/mL were associated with B-cell repopulation. Low levels of ocrelizumab ADAs were detectable in four patients (5.7%) with corresponding low ocrelizumab concentrations and start of B-cell repopulation.

Conclusion and discussion:

Serum ocrelizumab concentration was strongly associated with B-cell count. Measurement of ocrelizumab drug concentrations and ADAs could play a significant role to further personalise treatment and predict the start of B-cell repopulation in ocrelizumab treatment.

A higher red blood cell methotrexate polyglutamate 3 concentration is associated with methotrexate drug-survival in patients with Crohn's disease

MD Maartje van de Meeberg[1], MD, PhD Herma Fidder[2], MSc Janani Sundaresan[1], PhD Eduard Struys[1], MD, PhD Bas Oldenburg[2], MD Mares Wout[3], MD Nofel Mahmmod[4], MD, PhD Dirk van Asseldonk[5], MD Maurice Lutgens[6], MD, PhD Johan Kuyvenhoven[7], MD Svend Rietdijk[8], MD, PhD Loes Nissen[9], MD, PhD Parweez Koehestanie[10], PhD Robert de Jonge[1], MD, PhD Maja Bulatovic - Calasan[2], MD, PhD Gerd Bouma[1]

[1]Amsterdam UMC, Amsterdam, The Netherlands, [2]UMC Utrecht, Utrecht, The Netherlands, [3]Hospital Gelderse Vallei, Ede, The Netherlands, [4]St. Antonius Hospital, Nieuwegein, The Netherlands, [5]Noord west Hospital, Alkmaar, The Netherlands, [6]Elizabeth Tweesteden Hospital, Tilburg, The Netherlands, [7]Spaarne Gasthuis, Hoofddorp, The Netherlands, [8]OLVG, Amsterdam, The Netherlands, [9]Jeroen Bosch Hospital, Den Bosch, The Netherlands, [10]Bravis Hospital, Roozendaal, The Netherlands

Immunosuppression 2, Sal D, september 26, 2023, 13:00 - 14:30

Introduction

Predicting and monitoring methotrexate (MTX) responses in patients with Crohn's disease (CD) is presently not possible. Measurement of MTX-polyglutamates (MTX-PGs) in red blood cells (RBC) might enable therapeutic drug monitoring (TDM) as shown in other immune-mediated inflammatory diseases. Our aims were to assess the relation between MTX-PGs and treatment response, and to identify predictors of response in CD patients treated with MTX.

Materials and methods

In a multicenter prospective cohort study, CD patients starting subcutaneous (s.c.) MTX without biologics were included and followed for one year. At baseline, clinical and biochemical parameters were recorded. Eight ,12,24, and 52 weeks after start of therapy or when dropping out, blood samples were collected and individual MTX-PG levels (MTX-PG1 - MTX-PG5) were assessed in RBCs using mass spectometry. Primary outcome was either s.c. MTX discontinuation or initiation of step-up therapydue to disease activity or toxicity. MTX-PGs were analysed in an extended Cox model, and corrected for prednisone (at start) and budesonide. Secondary outcomes included biochemical disease activity, measured with fecal calprotectin (FCP).

Results

Eighty CD patients enrolled (mean age 55±13y, 35% male) with a median FCP of 268 µg/g (IQR 73-480). After one year 21 patients were still on MTX sc monotherapy. Twenty-one patients stopped MTX because of disease activity, 29 because of toxicity, and four because of a combination of both reasons (5 patients censored: ended study participation or stopped MTX because of undefined reasons).

MTX-PG3 was the most abundant MTX-PG species with a median concentration of 51 nmol/L RBC (IQR 37-62) at week 12. A higher MTX-PG3 concentration was associated with a higher rate of MTX drug survival (HR 0.86:for every 10 nmol/L increase in MTX-PG3 the rate of MTX discontinuation decreased with 14%, 95%CI 0.75-0.99), lower FCP (β -3.7, SE 1.3) as well as biochemical response (FCP < 250, OR 1.1, 95% CI 1.0-1.3).

A higher HBI at baseline was associated with an increased rate of s.c. MTX monotherapy discontinuation (HR 1.08, 95% CI 1.02-1.16). Predictors of discontinuation due to disease activity (cause specific hazards) were male sex (3.83, 1.62-9.05), baseline eGFR (1.06, 1.02-1.09),baseline HBI (1.12, 1.02-1.23) and baseline plasma folate (0.94, 0.88-0.99). Sex and plasma folate were not correlated with HBI. No toxicity-specific predictors for stopping MTX because could be identified.

Discussion and conclusions

RBC MTX-PG3 concentrations are related to better MTX drug-survival and decreased biochemical disease activity. Therefore, the measurement of RBC MTX-PG3 holds potential as a tool for TDM. Lower plasma folate at baseline and male sex are predictors for MTX-specific failure in the first year.

Methotrexate polyglutamate concentrations in target colonic mucosa, and white blood cells compared to non-target red blood cells of patients with Crohn's disease

MD Maartje van de Meeberg[1], MD Eduard Struys[1], Msc Marry Lin[1], MD, PhD Herma Fidder[2], Msc Janani Sundaresan[1], MD, PhD Bas Oldenburg[2], MD Wout Mares[3], MD Nofel Mahmmod[4], MD, PhD Dirk van Asseldonk[5], MD Maurice Lutgens[6], MD, PhD Johan Kuyvenhoven[7], MD Svend Rietdijk[8], MD, PhD Loes Nissen[9], MD, PhD Parweez Koehestanie[10], MD, PhD Gerd Bouma[1], MD, PhD Maja Bulatovic - Calasan[2], PhD Robert de Jonge[1]

[1]Amsterdam UMC, Amsterdam, Netherlands, [2]UMC Utrecht, Utrecht, The Netherlands, [3]Hospital Gelderse Vallei, Ede, The Netherlands, [4]St Antonius Hospital, Nieuwegein, The Netherlands, [5]Noord West Hospital, Alkmaar, The Netherlands, [6]Elisabeth Tweesteden Hospital, Tilburg, The Netherlands, [7]Spaarne Gasthuis, Hoofddorp, The Netherlands, [8]OLVG, Amsterdam, The Netherlands, [9]Jeroen Bosch Hospital, Den Bosch, The Netherlands, [10]Bravis Hospital, Roozendaal, The Netherlands

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Introduction

MTX polyglutamates (MTX-PGs) are generated during treatment with methotrexate (MTX), by the enzyme folylpolyglutamate synthetase (FPGS), which intracellularly catalyzes the additions of up to seven glutamate residues to MTX within 24 hours after administration. MTX-PG3 in red blood cells (RBC) show a concentration-effect relationship in patients with Crohn's disease (CD) and is therefore a potential tool for therapeutic drug monitoring. However, RBCs are neither effector cells in the pathophysiology of CD nor are they the target cells in the treatment of CD. The extent of variability of MTX-PGs in white blood cells (PBMCs), which are the effector cells, or in the intestinal mucosa, i.e. the target cells, have as of yet not been determined.

Materials and methods

In a multicenter prospective cohort study, CD patients were followed for 12 months upon the initiation of subcutaneous (sc) MTX therapy. Eight, 12, 24, and 52 weeks after start of therapy or when MTX was stopped, blood samples were collected. Mucosal biopsies were obtained from non-inflamed rectum and/or inflamed mucosa (if present) during a ileocolonoscopy for clinical purposes or rectoscopy for study purposes after 24 weeks. Individual MTX-PGs (MTX-PG1 - MTX-PG6) were analyzed in intestinal mucosa, RBCs and PBMCs by mass spectrometry (UPLC-ESI-MS/MS) using stable-isotope-labelled internal standards. In PBMCs, only MTX-PG1 to MTX-PG4 were measured.

Results

We collected 24 mucosal, 6 PBMC and 193 RBC samples during the follow-up of eighty CD patients. We were able to measure MTX-PG1-6¬ in all mucosa samples and MTX-PG1-4 in all PBMCs. MTX-PG6 was not detectable in RBC samples. The PBMC MTX-PG concentrations were higher than in matched RBCs (MTX-PG1 x18, PG2 x12, PG3 x3, PG4 x1.5). The prevalence of the MTX-PGs differed between the matrices: mucosa = PG1 (29%) > PG5 > PG4 > PG3 > PG2 > PG6 , PBMC = PG1 (48%) > PG2 > PG3 > PG4 , and RBC = PG3 (32%) > PG1 > PG4 > PG2 > PG5. The MTX-PG3 concentration was 60.9 (44.4 - 136.8) fmol/mg protein in mucosa, 12.8 (7.1 - 34.9) fmol/106 cells in PBMCs and 5.1 (3.9 – 7.1) fmol/106 cells in RBCs.

We collected three mucosal, three PBMC and 19 RBC samples after MTX discontinuation (2-10 weeks). We found a rapid and deep decline of MTX-PGs in PBMCs, but not in mucosa and RBCs. There was a non-significant decrease of long-chain MTX-PGs in contrast to the fast and significant decrease of short-chain MTX-PGs after MTX discontinuation.

Discussion and conclusions

This is the first time that MTX-PGs are measured in intestinal mucosal samples and PBMCs of CD patients. We found a different pattern of the MTX-PG species across the matrices, possibly due to differences in FPGS activity, life span of the cells or ongoing absorption. MTX-PG3 was not the most abundant species in the effector cell (PBMCs) and target cells (mucosa). However, the MTX-PG3 concentration is three times higher in PBMCs than in RBCs. Whether MTX-PG3, measured in PBMCs and mucosa, displays a clear concentration-effect relationship is presently unknown.

Risperidone-induced weight gain and alterations in appetite hormones in children and adolescents with autism spectrum disorder

Kajie Liang[1,3], PhD B.C.M. de Winter[1,3], MD R.A. Hermans[1,2,3], MD, PhD S.M. Kloosterboer[2], PharmD I. Bayraktar[1], Professor M.H.J. Hillegers[2], Phd S.A.A. van den Berg[4], PhD B.C.P. Koch[1,3], MD, PhD Bram Dierckx[2]
[1]Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, The Netherlands, [2]Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Center, Rotterdam, The Netherlands, [3]Rotterdam Clinical Pharmacometrics Group, Erasmus University Medical Center, Rotterdam, The Netherlands, [4]Department of clinical chemistry, Erasmus MC, University Medical Center, , The Netherlands

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Background
Risperidone, while efficacious in reducing irritability and hyperactivity in children with autism spectrum disorder (ASD), is associated with significant weight gain and increased risk of Diabetes Mellitus. Although weight gain is multifactorial, metabolic and endocrine changes may play an essential role in this process. This study explores the association between appetite hormones and weight gain over time in relation to risperidone exposure.

Methods
In the prospective SPACe study, we collected blood samples in risperidone-treated children with ASD. In addition to the risperidone and 9-OH-risperidone levels (sum trough concentration), we determined the appetite hormones leptin, bioleptin, neuropeptide-Y (NPY), gastric inhibitory peptide (GIP), insulin, and glucose levels at the fasting state, before the start, and at 12 and 24 weeks of treatment. We used Wilcoxon's two-tailed signed-rank test to evaluate the differences in the parameters between distinctive time points.

Results
Seventeen patients (71% boys, mean age 10.38 yr, and mean body weight 31.8 kg) were included. Significantly elevated levels of bioleptin and insulin, and homeostasis model assessment insulin resistance index* ($p<0.05$) were found in the first 12 weeks, followed by a trend toward a plateau at 24 weeks. Differences in leptin, NPY, and GIP levels were not significant. A concomitant increase in the risperidone sum trough concentration, and BMI z-score was observed ($p<0.05$).
* Homeostasis model assessment insulin resistance index: gives an estimation of insulin sensitivity (balance between hepatic glucose output and insulin secretion)

Discussion/Conclusion
In risperidone-treated children and adolescents, we observed alterations in appetite hormones over the course of treatment. We contend that these changes can play a role in weight gain under antipsychotic treatment. These findings warrant future research.

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Method development for investigating the excretion of selected drugs into exhaled breath

Ms. Juel Maalouli Schaar[1], Dr. Lea Wagmann[1], Prof. Olof Beck[2], Prof. Markus R. Meyer[1]
[1]Department of Experimental and Clinical Toxicology, Institute of Experimental and Clinical Pharmacology and Toxicology, Center for Molecular Signaling (PZMS), Saarland University, Homburg, Germany , [2]Karolinska Institute, Clinical Neuroscience , Stockholm, Sweden

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Introduction.
Human exhaled breath (EB) as non-invasive sample matrix was shown to be suitable for the detection of volatile as well as non-volatile compounds. Amongst the non-volatile compounds detected in EB were also drugs and drugs of abuse. As previous studies were mainly focused of methods for the analysis of drugs of abuse in EB, the current study aimed to develop an analytical workflow for the qualitative detection of selected drugs in EB. The analytical procedure should be based on liquid chromatography (LC) coupled to high-resolution mass spectrometry (HRMS). Analytes were selected to cover different drug classes such as antihypertensives (e.g., bisoprolol), anticonvulsants (e.g., pregabalin), benzodiazepines (e.g., lorazepam), and opioid analgesics (e.g., tramadol).

Materials and Methods.
The Breath Explor Sampling Devices offering three separate collectors were used for blank EB collection. The collector surface was then fortified with amounts of up to 10,000 pg for each analyte. Rinsing of the collector surface with 3 mL methanol as extraction solvent and repeated centrifugation was used for eluting the analytes from the sampling devices. The solvent was then evaporated to dryness under nitrogen and gentle heating at 70°C. After reconstitution of the dry residue using a mixture of mobile phases (1:1, v/v), a volume of 10 µL was injected onto the LC-HRMS/MS system. The used column was a Waters Acquity UPLC BEH C18 (1.7 µm, 2.1 mm x 100 mm) and the mobile phases consisted of 2 mM aqueous ammonium formate containing acetonitrile (1%, v/v) and formic acid (0.1%, v/v, pH 3, eluent A), as well as 2 mM ammonium formate solution with acetonitrile:methanol (1:1, v/v) containing water (1%, v/v) and formic acid (0.1%, v/v, eluent B). The Orbitrap-based MS (Thermo Fisher Scientific Q Exactive) was operated in positive electrospray mode.

Results.
Bisoprolol, bromazepam, carbamazepine, O-desmethyltramadol, diazepam, lorazepam, metoprolol, nordazepam, nortilidine, ramipril, ramiprilat, tapentadol, tilidine, tramadol and pregabalin could qualitatively be detected using the described procedure. The limits of detection (LOD) ranged from 100 pg/collector to 10,000 pg/collector. The method was found to be selective for all analytes and no carry-over was observed. There were only minor matrix effects and a reproducible recovery for all analytes was observed.

Discussions and Conclusions.
A workflow for the qualitative detection of selected drugs in EB was successfully developed. The sample preparation and the analytical part is straightforward and thus time- and cost-efficient. After further investigations including validation for quantitative analysis according to international guidelines, proof-of-concept studies using real samples to investigate the actual excretion of drugs/metabolites in EB will follow. The method might then be used in a clinical toxicology setting e.g., for adherence monitoring or other drug monitoring programs.

Target attainment of fludarabine exposure in adult allogeneic hematopoietic stem cell transplantation: conventional versus model-informed precision dosing

Msc Tim Bognàr[1], Dr. K. C. M. van der Elst[1], Dr. A Lalmohamed[1,2], Prof. Dr. A C G Egberts[1,2], Dr. A H M de Vries Schultink[1], Dr. D J A R Moes[3], C A Nijssen[4], Dr. P M van de Ven[5], Dr. M A de Witte[4], Prof. Dr. J H E Kuball[4,6]

[1]Department of Clinical Pharmacy, University Medical Center Utrecht/Wilhelmina Children's Hospital, Utrecht, the Netherlands, [2]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands, [3]Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, the Netherlands, [4]Department of Hematology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands, [5]Department of Data Science and Biostatistics, Julius Center for Health Sciences and Primary Care, Utrecht, the Netherlands, [6]Center for Translational Immunology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

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Introduction:
Fludarabine is currently being used in conditioning regimens in allogeneic hematopoietic stem cell transplantation (HCT) for the treatment of (non)-malignant diseases. Fluctuations up to sixfold in plasma exposure of F-ara-A, the metabolite of fludarabine, have been observed among patients, and clinical outcomes have been associated with fludarabine exposure. Model-informed precision dosing (MIPD) of fludarabine may therefore optimize exposure in patients, possibly leading to improved treatment outcomes. The objective of this interim analysis was to evaluate the effect of MIPD on fludarabine target attainment.

Methods:
In this multicenter, open-label, phase II, randomized controlled trial (EudraCT number: 018-000356-18), we included patients of 18 years and older with hematological malignancies with an indication for an allogeneic HCT. All patients received the conditioning regimen consisting of anti-thymocyte globulin, busulfan (target area under the curve from first dose to infinity (AUC0–∞) of 85-95 mg*h/L) and fludarabine. Patients were randomized to one of two treatment arms; those in the conventional dosing arm were dosed with 160 mg/m2 fludarabine over 4 consecutive days, while those in the MIPD arm were dosed with 40 mg/m2 fludarabine on day 1, with day 1 concentration-guided MIPD on days 2, 3 and 4. Primary outcome was the proportion of patients with target exposure attainment of fludarabine (target AUC0–∞ of 15-25 mg*h/L) in the MIPD group vs. the conventional dosing group (Fisher's exact test). Secondary objectives were the variance in fludarabine exposure between both groups (F-test for equality of variances) and predictors for fludarabine overexposure (AUC0–∞ >25 mg*h/L) in patients with conventional dosing (univariate logistic regression analysis or the Fisher's exact test). Potential predictors were predefined based on biological plausibility and available literature. The AUC0-∞ was estimated using nonlinear mixed effect modeling with a previously published fludarabine population pharmacokinetic model.

Results:
In total, 1.0% (n=1/102) of patients were underexposed, 10.8% (n=11/102) were overexposed, and 88.2% (n=90/102) were optimally exposed to fludarabine. In the conventional dosing arm, 75.5% (n=37/49) of patients attained their fludarabine exposure target, while in the MIPD arm 100.0% (n=53/53) attained their target (p<0.0001). The variance of the AUC0–∞ in those with conventional dosing (range 13.8–37.0 mg*h/L, mean=22.7, SD=5.7) was significantly greater than the variance of the AUC0–∞ in those with MIPD (range 18.1–24.3 mg*h/L, mean = 20.0, SD=1.3, p<0.0001), while the median AUC0–∞ was similar between both groups (19.9 vs. 19.6 mg*h/L, respectively). In patients with conventional dosing, univariate predictors for overexposure were the female gender (39.1% vs.

7.7%, OR=7.7, 95% CI 1.5-40.9) and age >50 years (29.7% vs. 0.0%, p=0.045). Although renal impairment (eGFR <90 ml/min) was not found to be a significant predictor, it showed a trend towards increasing the risk of overexposure (31.3% vs. 18.2%).

Discussion and conclusion:
MIPD of fludarabine improved target attainment compared to conventional dosing by reducing the variance of the exposure. To prevent fludarabine overexposure, MIPD may be beneficial, particularly in females, patients of 50 years and older and potentially in those with renal impairment.

Digital PCR and Nanopore sequencing: a promising combined approach for CYP2D6 genotyping

Amandine Etcheverry[2], Regis Bouvet[2], Florent Denoual[2], Christele Dubourd[2], Marie-Clémence Verdier[1], Marie-Dominique Galibert[2], Dr Camille Tron[1]
[1]Pharmacology department, Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) UMR_S 1085, F-35000 Rennes, France, Rennes, France, [2]Department of Molecular Genetics and Genomics, Rennes Hospital University, Rennes, France., Rennes, France

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction:
Cytochrome 2D6 (CYP2D6) gene coding for an enzyme involved in metabolism of 25% of drugs, is a very important pharmacogene known to be highly polymorphic. To be able to elucidate the phenotype of the enzyme (poor/intermediate/normal/ultrarapid metabolizer), genotyping assays must include identification of dozens of variants alleles including nucleotide deletions, single nucleotide polymorphisms, copy number variations as well as hybridization with CYP2D7. To get a complete genotyping of CYP2D6, multiplex assays such as next generation sequencing or DNA microarrays are usually used but may be challenging to implement in labs with middle throughput since it requires expensive reagents and instruments as well as specific skills to interpret results. To overcome these hurdles, we performed a pilot study to assess interest of alternative genotyping assays based on digital PCR and Nanopore sequencing.

Material and Methods:
Twenty-four reference samples from Coriell Institute were selected, as they were representative of the CYP2D6 variants to be included in Pharmacogenetics (Pgx) genotyping assay, as recommended by a consensus of Pgx learning societies (1). For each sample, two amplicons were generated: a 6.6 kb amplicon containing the CYP2D6 gene and a 5 kb amplicon specific from the CYP2D7-D6 fusion genes. Amplicons were sequenced using the Nanopore Native Barcoding Kit 24 V14 on a single R.10.4.1 Minion Flow cell (Oxford Nanopore Technologies) (2). DNA sequences were analyzed (alignment with Minimap, basecalling with Clair3, phasing with WhatsHapp and Copy number variation (CNV) analysis) to determine each sample diplotype. For samples with ambiguous diplotype (only one genotype sequenced), digital PCR on Naica® System (Stilla technologies) was used to accurately quantify the CNV status and precise the diplotype.

Results:
Nanopore sequencing provided a very high quality of sequencing with a fast and simple workflow. The combination with digital PCR allowed accurate characterization of CYP2D6 CNV confirming the number of copies (1, 2, 3 and 4) of reference samples. The workflow of digital PCR was fast and flexible. Both approaches appeared compatible with scalable genotyping yield which is convenient to adapt to the irregular number of clinical requests while keeping a fast turnaround time of Pgx result (i.e. every week).

Discussion-Conclusion:
We reported an original and innovative application to Pharmacogenetics of Nanopore sequencing combined with digital PCR. Both technologies provide accurate results for reference DNA samples including tier 1 and tier 2 CYP2D6 alleles. In addition to this proof of concept, a more extensive validation of the assays is underway in our center with a view to implement these genotyping approaches of CYP2D6 in clinical routine.

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The pharmacokinetic profile of olanzapine in anorexia nervosa patient: a case report

Kajie Liang[1], PharmD, PhD L.L. Krens[1], MD, PhD J.J.B. van der Vlugt[2], PharmD, PhD T.M. Bosch[1,3]
[1]Department of Hospital Pharmacy, Maasstad Hospital, Rotterdam, The Netherlands, [2]Antes Parnassia Group, Psychiatric Hospital, Rotterdam, The Netherlands, [3]Department of Clinical Pharmacology & Toxicology MaasstadLab, Maasstad Hospital, Rotterdam, The Netherlands

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Introduction
The effect of olanzapine in the treatment of anorexia nervosa (AN) has been noted in several studies.1,2 AN is characterized by altered body composition due to extremely low body weight, which may impact several pharmacokinetic processes. The absence of pharmacokinetic studies of olanzapine in AN patients hampers the optimization of the treatment. Clinicians often adopt a start low stay low dosing regimen for olanzapine, especially in patients with the lowest BMIs. This is likely to result in subtherapeutic treatment and contribute to an even poorer treatment prognosis. Our main objective is to gain insight into the pharmacokinetics of olanzapine in AN patients in order to optimize precision dosing.

Materials and methods
To date, we report the case of a severely catechetic 38-year woman, diagnosed with anorexia nervosa according to DSM-IV criteria. Due to severe malnutrition and deficiencies caused by a restrictive eating disorder, she was admitted for enteral feeding. As a result of disease progression, olanzapine was initiated to reduce anxiety, agitation, and to mitigate anorectic obsession. The dosage was titrated from 2.5mg to 10mg once daily. At steady states, we assessed the olanzapine serum levels by a limited sampling method to calculate the total drug exposure (AUC0-24hr) and the pharmacokinetic parameters of olanzapine.

Results
The BMI of the patient was restored from 12 (anorexic) at admission to 18.9 (normal) six months after intensive psychotherapy, dietetic interventions, and concomitantly pharmacotherapy with olanzapine. Based on EDE-Q and Y-BOCS assessments, clinical improvements of 87 and 19 scoring points were observed over a period of six months. Regarding the pharmacokinetics of olanzapine, the measured trough levels of olanzapine were 6, 4, and 16 µg/L at steady state for the respective daily doses of 2.5mg, 5mg, and 10mg. The observed drug clearance was 7.5, 10.2, and 11.6 L/hr, the volume of distribution was 11.3, 12.8, and 16.5 L, and the calculated total exposures (AUC0-24h) were 200.5, 147.3, and 517.5 µg/L*h, the Tmax 4, 6, and 6 hours, and the half-life 22.2, 15.1 and 20.1 h were for the respectively given dosages.

Discussions and conclusions
In the absence of a therapeutic window for the indication anorexia nervosa, we can only conclude that the trough concentrations are on the lower end in comparison to the therapeutic levels observed in the treatment of schizophrenia (20 – 80 µg/L).3 The given dosage of 10mg olanzapine was well tolerated by this patient and resulted in a trough level of 16 µg/L. Future research is needed to gain more insight into the pharmacokinetics in this population to define a therapeutic window for the indication AN in order to optimize precision dosing in this vulnerable group of patients.

Dietary supplements and nutraceuticals – what, how and why (not)

MD Henrik Magistad Knutrud[1]
[1]Department of Clinical Pharmacology, Oslo University Hospital, Oslo , Norway

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction
Food and plants have been used in medicine for millennia - early examples being ubiquitous remedial use of honey in ancient Egypt and traditional Chinese use of ma huang both for asthma and for performance enhancement.

Globally, the interest in dietary supplements is strong. A 2022 survey showed that 75% of Americans use some form of supplement daily. A 2020 survey from Norway reported similar results - 71% daily users of one or more supplements and around 10% having used herbal or plant-based medicines the past year. The supplement industry is exceptionally lucrative with a global market size estimated to USD 163,986 million, with further rapid growth expected. Interestingly, 77% of Americans find the supplement industry trustworthy according to the 2022 CRN/Ipsos survey (contrasted to 23% for the pharmaceutical industry). This review will give a short and concise update on the current trends in supplementation.

Materials and methods
Current literature on the subject of dietary supplements and nutraceuticals was reviewed and summarized, based on individual searches in PubMed and dedicated databases such as the Natural Medicines Research Collaboration and Examine.com. Relevant supplements were identified by survey popularity and search rankings. Substances were classified according to their intended effect into the following groups: 1. Athletic performance 2. Brain health (including mood and sleep) 3. Immune response and pain 4. Healthy aging and longevity and 5. Hormonal health. Potential mechanisms of action were summarized based on available evidence. Lastly, serious adverse effects and drug interactions relevant to patient treatment were highlighted.

Results
Data for 30 dietary supplements and nutraceuticals were reviewed. The most popular supplements were several types of vitamins and minerals, fish oil, protein formulations and plant extracts. In many cases, the mechanism of action was not fully elucidated and data was limited. Many supplements span multiple groups of intended effect.

Conclusions and discussion
The practice of supplementation remains controversial and polarizing. While some supplements may have benefits in certain situations, others are of dubious benefit. For many people, supplements grant a sense of empowerment and responsibility in an era where maintaining or improving personal health is a focus point. However, the pitfalls are many and not always easily identified: the evidence for the effect of many supplements is sub-par at best, and completely lacking at worst, as this review confirmed. Many consumers are unaware of the adverse effects of supplements and interactions with medications, and patients rarely disclose supplement use to their physicians. In addition, the supplement industry is rife with quality control issues, and impurities and contamination have led to massive scale injury and death.

The apparent potential of dietary supplements calls for better regulation and higher quality research. In the meantime, it is important that healthcare providers maintain an overview of the relevant supplements, and their clinical implications and potential health risks. It is also prudent to understand why a patient might be motivated to use a particular supplement.

Influence of antigen mass on the pharmacokinetics of rituximab in chronic lymphocytic leukemia

Mr Olivier Le Tilly[1], Mrs Caroline Dartigeas[1], Mr David Ternant[1]
[1]CHRU de Tours, Université de Tours, Tours, France

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction
Rituximab is an anti-CD20 antibody used in the treatment of chronic lymphocytic leukaemia (CLL) with fludarabine and cyclophosphamide (FCR protocol). A previous study (1) showed an improvement in progression-free survival in elderly patients receiving maintenance treatment with rituximab 500 mg/m² every two months. From a subset of 69 patients from this study, our objective was to investigate the pharmacokinetics of rituximab and then to analyse the exposure-efficacy relationship.

Materials and Methods
Trough and peak concentrations of rituximab were measured during the FCR cycles and then during the maintenance treatment in the patients concerned. The pharmacokinetics of rituximab was studied using a population approach. The covariates studied were (at inclusion) gender, age, weight, body surface area, white blood cell count, albumin, Binet stage, lymph nodes size, presence of splenomegaly and del11q22 . The selection of covariates was done using the likelihood ratio test with a stepwise approach. Progression-free survival (PFS) and overall survival (OS) were studied using a log-rank test (univariate qualitative) and then Cox model (multivariate) with a stepwise approach.

Results
Of the 69 patients included (median age: 71), 41 received FCR alone and 28 received rituximab maintenance. The model used was a two-compartment model with target-mediated drug disposition (TMDD model with constant target and irreversible binding approximations), influenced by the presence of splenomegaly (p=0.0088) and Binet C stage (p=0.0009). Covariates influenced the first concentrations most and had little influence during maintenance, with a convergence of the different pharmacokinetic profiles over time. Rituximab exposure between two injections (AUCτ) during maintenance was similar to that observed at the end of FCR treatment.
PFS and OS were longer in patients with a minimum target concentration lower than median (Log-rank: p=0.024 and 0.031, respectively). Multivariate analysis did not improve the description of PFS and age also influenced OS.

Discussions and Conclusions
While most studies of rituximab in CLL use models with a time-varying clearance, we used a target-mediated drug disposition model (2-4). Our approach was semi-mechanistic and the covariates influencing the pharmacokinetics of rituximab accounted for bone marrow and peripheral antigenic mass.
The concentration-efficacy relationship of rituximab in CLL is poorly rapported. Our approach would further explore this relationship by looking at the antigenic mass estimated using rituximab concentrations. The implications for interventional research have yet to be evaluated.

1 : Dartigeas C et al. Rituximab maintenance versus observation following abbreviated induction with chemoimmunotherapy in elderly patients with previously untreated chronic lymphocytic leukaemia (CLL 2007 SA): an open-label, randomised phase 3 study. Lancet Haematol. feb 2018;5(2):e82-94.
2 : Li J et al. Population pharmacokinetics of rituximab in patients with chronic lymphocytic leukemia. J Clin Pharmacol. dec 2012;52(12):1918-26.

3 : Assouline S et al. Pharmacokinetics and safety of subcutaneous rituximab plus fludarabine and cyclophosphamide for patients with chronic lymphocytic leukaemia. Br J Clin Pharmacol. nov 2015;80(5):1001-9.
4 : Lavezzi SM et al. Systemic Exposure of Rituximab Increased by Ibrutinib: Pharmacokinetic Results and Modeling Based on the HELIOS Trial. Pharm Res. may 2019;36(7):93.

Linezolid concentration-toxicity relationship: looking back on ten years of therapeutic drug monitoring

Dr Sébastien Lalanne[1], Dr François Bénézit[2], Pr Eric Bellissant[1], Dr Florian Lemaitre[1], Dr Marie-Clémence Verdier[1]
[1]University Hospital of Rennes, Laboratory of Clinical Pharmacology, 35000 Rennes, France, Rennes, France, [2]University Hospital of Rennes, Department of infectious diseases, 35000 Rennes, France, Rennes, France

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Linezolid (LNZ) is routinely used for the treatment of Gram-positive infections and multidrug-resistant tuberculosis (TB). Myelotoxicity, neuropathies and hyperlactatemia are severe adverse drug reactions (ADRs) induced by LNZ. LNZ therapeutic drug monitoring (TDM) is frequently performed to avoid these ADRs but concentration-toxicity relationship is heterogeneously documented.

This 10-years monocenter retrospective study included all patients benefiting from LNZ TDM. LNZ plasma concentrations were determined using liquid chromatography with UV detection. Infectious context (non-TB versus TB), dosage, renal clearance, mention of ADRs attributed to LNZ at the time of sampling (myelotoxicity, neuropathy, hyperlactatemia) were gathered. Cmin were compared within the two groups according to the presence or not for each ADR.

Between 2012 and 2021, 62 patients (43 non-TB, 19 TB) were included, 83 Cmin were measured. For non-TB group, 91% were treated by 600 mg BID and 78% in the TB group were treated with 600 mg OD. The most frequent ADR was hyperlactatemia (32%) followed by hematotoxicity (26%) and neuropathy (6%), leading to definite discontinuation of LNZ for 18 patients. Mean Cmin were significantly lower in TB (2.5±1.6) than non-TB (9.0±9.2) mg/L group ($p<0.05$). The most frequent AE was hyperlactatemia (32%) followed by haematotoxicity (26%). Neuropathy occurred in a minority of patients (6%). The incidence of hematotoxicity was higher in TB than in non-TB group. However, Cmin were below the hematotoxicity threshold of 7 mg/L (1) in the TB group and not significantly different between patients with and without hematotoxicity. In the non-TB group, mean Cmin was 17 mg/L in patients with hematotoxicity, significantly above 7 mg/L threshold. Cmin were not different according to the respective occurrence of AE “neuropathy" and "hyperlactatemia" or not in the 2 groups.
LNZ Cmin remain highly variable and consistent with the hematotoxicity threshold for non-TB patients. This threshold does not appear to be appropriate in the TB group, with lower exposure and high frequency of ADRs attributed to LNZ. These results raise the question of the existence of confounding factors for TB patients and the choice of optimal dosing in TB, suggesting that a threshold of toxic exposure may already be reached at 600 mg/d. This threshold remains to be characterized with a prospective trial with systematic TDM and concomitant assessment of LNZ imputability.

(1) M. H. Abdul-Aziz et al., « Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper », Intensive Care Med., vol. 46, no 6, p. 1127-1153, 2020, doi: 10.1007/s00134-020-06050-1.

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Establishing a pharmacokinetic model for rituximab in multiple sclerosis

Trond Trætteberg Serkland[1,2], Silje Skrede[1,2], Erik I Hallin[1], Kjell-Morten Myhr[3,4], Øivind Grytten Torkildsen[3,4], Susanna Röblitz[5]
[1]Department of Medical Biochemistry and Pharmacology, Bergen, Norway, [2]Department of Clinical Science, University of Bergen, Bergen, Norway, [3]Neuro-SysMed, Department of Neurology, Haukeland University Hospital, Bergen, Norway, [4]Department of Clinical Medicine, University of Bergen, Bergen, Norway, [5]Computational Biology Unit, Department of Informatics, University of Bergen, Bergen, Norway

Biologicals, Sal B, september 26, 2023, 13:00 - 14:30

INTRODUCTION
Rituximab is a monoclonal antibody (mAb) directed against the CD20 antigen on the surface of B-lymphocytes. Originally approved by the U.S. FDA in 1997 to treat patients with B-cell non1Hodgkin lymphoma, the number of approved indications for rituximab has steadily increased. In addition, there has been growing interest in the use of off-label rituximab in the management of a variety of disorders.

Multiple sclerosis (MS) is a chronic immune-mediated disease causing central nervous system lesions with demyelination and axonal damage. Rituximab efficiently suppresses inflammatory disease activity in relapsing-remitting MS. However, the optimal dosage and treatment interval is not known.

To explore whether a pharmacokinetic model may contribute to clarification of this issue, we established a clinical pharmacological observational sub-study, “Rituximab and Ocrelizumab in Serum from patients with Multiple Sclerosis” (ROS-MS), to an ongoing clinical trial, “Ocrelizumab VErsus Rituximab Off-Label at the Onset of Relapsing MS Disease” (OVERLORD-MS).

MATERIALS AND METHODS
Patients with newly diagnosed MS received rituximab infusions every 6 months. Blood samples were drawn pre and post infusion (Cmax), and after 2, 4, 8, 12 and 24 weeks. Quantification of serum rituximab was performed using a recently established liquid chromatography tandem mass spectrometry method. In addition, a number of biochemical and clinical parameters were monitored.

To our knowledge, only one PK model for rituximab in non-cancer indications (anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)) has been published. We examined whether this model can be used to denote the pharmacokinetics of rituximab in the treatment of MS.

RESULTS
Results indicate that the pharmacokinetic properties of rituximab in MS treatment can be described using a semi-mechanistic two-compartment model including a latent target antigen turnover, in alignment with the previously published model. Hence, such a model allows for an estimation of specific target-mediated elimination along with non-specific elimination.

DISCUSSIONS AND CONCLUSIONS
We aim at developing a model describing PK properties of rituximab used in treatment of MS, exploring whether such a model could provide support in the determination of an adequate dosage and treatment interval to deliver personalized treatment.

Point-of-Care Therapeutic Drug Monitoring of chemotherapy from microvolume blood samples with a specifically designed microfluidic system

Dr András Füredi[1,2], Dóra Bereczki[1,2,3], Balázs Gombos[2], Ines Lidia Haffaressas[2], Dr Pál Szabó[4], Dr Péter Vajdovich[5], Dr Péter Fürjes[1]
[1]Microsystems Laboratory, Centre For Energy Research, Institute Of Technical Physics And Materials Science, Budapest, Hungary, [2]Institute of Enzymology, Research Centre for Natural Sciences, Budapest, Hungary, [3]Doctoral School on Materials Sciences and Technologies, Óbuda University, Budapest, Hungary, [4]Centre for Structural Sciences, Research Centre for Natural Sciences, Budapest, Hungary, [5]Department of Clinical Pathology and Oncology, University of Veterinary Medicine, Budapest, Hungary

Oncology, Møterom 2, september 25, 2023, 13:00 - 14:30

Cancer claims almost 10 million lives annually, making it one of the major causes of death around the world. Despite the development of novel drugs and treatment options, the 5-years survival of the most common cancers are still strikingly low. Chemotherapy (CT) is a widely used option to treat malignancies, however CT protocols are established on a “one size fits all” basis and ignore inter-patient differences in drug pharmacokinetics which influence the blood levels of anticancer drugs, therefore leading to improper dosing in 50% of patients. Missing the target blood concentration will lead to drug resistance and/or unwanted side effects. Therapeutic Drug Monitoring (TDM) could be the key to improve and personalize CT, however the lack of an affordable point-of-care (POC) method is preventing its introduction to oncology. Mass spectrometry (MS) is the golden standard analytical approach to determine blood drug levels, but the instrument and specialized expertise to operate it are rarely available in the clinical environment. The high volume of blood required for MS analysis is also a challenge, because cancer patients are regularly weakened. Exploiting the strong and specific fluorescence of anthracyclines, the most used CT agents, we developed a radically new microfluidic chip-based approach to rapidly determine plasma concentrations of several widely applied anticancer drugs and validated it with clinically relevant mouse models of cancer and samples obtained from veterinary oncology patients.
First, the fluorescent properties of several anthracyclines were determined in a concentration dependent manner in spiked phosphate buffered saline, fetal bovine serum and freshly isolated mouse plasma in 96-well plates using a fluorescent plate reader (Tecan Spark). Then, the same experiment was repeated in our POC-TDM microfluidic chip to investigate the effects of the microfluidic environment (decreased size of the measurement chamber and sample volume). While the sensitivity was the same, we were able to radically reduce the required volume of the sample from 100µl to 7µl. To validate whether our approach could work in vivo we used healthy FVB mice treated with the maximum tolerable dose of doxorubicin (DOX) and pegylated liposomal doxorubicin (PLD), took blood samples at several timepoints, isolated plasma, pretreated them to precipitate proteins and measured the samples with the POC-TDM chip and with MS as benchmark. The experiment was also done using a genetically engineered mouse model of triple negative breast cancer. Finally, the POC-TDM chip based method was tested in the clinical setting using periodically taken blood samples from feline patients treated with DOX or PLD.
Our POC-TDM method is quick, cheap and doesn’t require any specialized equipment to monitor the concentrations of CT drugs in the patients’ circulation. This new technology could help introduce routine TDM in oncology, open new avenues to investigate the inter-patient differences in drug metabolism and to design wearable cancer treatment devices.

Exploring the association between intra patient variability in trough concentration of pazopanib and clinical outcome in mRCC patients

Drs. Amy Rieborn[1], dr. Tom van der Hulle[2], prof. dr. Hans Gelderblom[2], prof. dr. Teun van Gelder[1], dr. Dirk Jan Moes[1]
[1]Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, Netherlands, [2]Department of Medical Oncology, Leiden University Medical Center, Leiden, Netherlands

Oncology, Møterom 2, september 25, 2023, 13:00 - 14:30

Introduction:
Pazopanib is an oral tyrosine kinase inhibitor (TKI), which is used as first line treatment in patients with metastatic renal cell carcinoma (mRCC) and as second line treatment in patients with soft tissue sarcoma (STS). By inhibition of the VEGF receptor, pazopanib downregulates angiogenesis, leading to inhibition of tumor growth. There is a well-established exposure-response relationship: pazopanib plasma through concentrations higher than 20 mg/L are associated with improved progression-free survival (PFS) in RCC patients. Pazopanib has a high interindividual variability in the pharmacokinetics (PK) and pharmacodynamics (PD). Standard dose regimen of 800 mg once daily is often adequate, however a considerable part of the patients are at risk of undertreatment or toxicity. Therefore, therapeutic drug monitoring (TDM) is likely to be of benefit for patients receiving pazopanib. Previous studies showed pazopanib has a moderate intra-patient variability in pharmacokinetics (IPV) compared to other TKIs, with a mean IPV of 24.7%. Non-adherence and food interactions are part of the explanation of this IPV, while other causes remain unclear. In disease areas such as transplantation medicine, high IPV of tacrolimus has previously been associated with poor outcome and is used as a prognostic biomarker. The relationship between IPV and clinical outcome has not been established in patients using pazopanib. Therefore, the aim of this study is to explore the relationship between pazopanib intra-patient variability and clinical outcome (PFS and/or OS) in both RCC and STS patients.

Methods:
Data from patients with RCC and STS treated with pazopanib and of whom pazopanib levels were monitored as part of routine clinical care between July 2016 and July 2022 at Leiden University Medical Center were available. Only patients from whom at least 3 pazopanib trough concentrations were available were eligible for the primary analysis. Baseline characteristics, pharmacokinetics (PK) (pazopanib concentrations, treatment schedule, dose adjustments, duration of treatment, comedication interacting with pazopanib), PD data (diagnosis, IMDC criteria, progression free survival, overall survival) were collected from electronic patient files with the help of CTcue. Dose corrected estimated trough concentrations were used to calculate IPV. IPV was calculated as coefficient of variation. The relationship between IPV and patients' PFS and OS was characterized with a Cox proportional hazards model.

Results:
In total, data of 150 patients treated with pazopanib was available, of whom 74 were eligible for primary analysis. In the primary analysis group, 54 patients were diagnosed with mRCC and 20 patients with STS. Median PFS was 10.0 months (range 1.4 – 81.9 months) and median OS was 18.5 months (range 1.4 – 81.9 months). Median dose-corrected IPV was 30.1% (range 6.4 – 85.9%). Cox proportional hazards model showed a trend towards worse PFS in the high IPV group (HR 1.5365, 95% CI 0.841 – 2.809, p = 0.163), as well as for OS (HR 1.372, 95% CI 0.6746 – 2.792, p = 0.38).

Discussion and conclusion:
In this exploratory analysis, high IPV shows to be a potential biomarker for therapy failure. More research in a larger dataset is warranted to confirm the present findings.

Impact of TDM of Biologics in the real-world, lessons learned and future perspectives

PhD Floris Loeff[1], PhD Karien Bloem[1], MD, PhD Gertjan Wolbink[2], PhD Theo Rispens[3], PhD Annick de Vries[1]
[1]Sanquin Diagnostic Services, Amsterdam, the Netherlands, [2]Amsterdam Rheumatology and Immunology Center, location Reade, Department of Rheumatology, Amsterdam, the Netherlands, [3]3. Department of immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, Amsterdam, the Netherlands

Biologicals, Sal B, september 26, 2023, 13:00 - 14:30

Biologics profoundly improve the quality of life (QoL) of patients in various disease areas. This primarily impacted on rheumatology and gastroenterology, but also cardiology, oncology, dermatology and neurology. Therapeutic drug monitoring (TDM) is vitally important to optimise therapy for all patients treated with biologics, it brings both under- and overtreatment to light. Monitoring of drug levels and determination of anti-drug antibodies (ADA) is relevant as it can guide clinical decisions to optimise treatment efficacy and cost effectiveness.

With our growing portfolio of PK/ADA assays (currently for 25 biologics) that we provide for service testing in the routine hospital diagnostic setting and for (academic) studies we can demonstrate the value of TDM in different medical areas with real-world data identifying treatment failure, overdosing, and effects of dose/interval changes.

We will provide real-world examples in which we collaborated with partners to establish the clinical implications of certain levels of biologics in a variety of disease settings. We elaborate on the impact of testing strategy and technique on the interpretation of generated results. Based on the experience we gained co-authoring more than 250 peer reviewed publications on TDM of biologics we share the lessons we learned trying to find the therapeutic window in various challenging settings. Conceptual difference and similarities between various biologics will be discussed.

For most biologics, reported incidences of ADA vary widely due in part to differences in assay technology. From our experience, measurement of functional drug levels circumvents this problem. Only in case significant impact on PK is suspected, ADA measurement needs to be considered to determine whether switching to a different biologic (with the same target) or a higher drug dose would benefit the patient. Or to determine compliance.

The need for regular injection i.v. or s.c. impacts negatively on the QoL. Also biologics belong to the most expensive drugs available. It is therefore key that biologics are to be applied with the lowest frequency as possible and in the most sensible and a cost-effective manner without losing clinical efficacy. We demonstrate that TDM based interval extension is safe in case of over-treatment in patients treated for rheumatoid arthritis, multiple sclerosis, and atopic dermatitis.

Retrospective data analysis of a multi-drug screen panel by LC-MS/MS used to support testing for the Emergency Department

Kamisha Johnson-Davis[1]
[1]University of Utah / ARUP Laboratories, , United States

Toxicology -clinical and environmental, Sal C, september 26, 2023, 13:00 - 14:30

Introduction:
In the United States, it is estimated that ~6000 Americans visit the emergency department daily, due to adverse drug reactions, resulting in 350 deaths each day. The risk for adverse drug reactions can increase with poly-drug therapy, intentional and accidental overdose, and illicit drug use. The purpose of this study was to develop a multi-drug screen panel by mass spectrometry as a testing option to support hospital emergency departments and review drug detection positivity rates. Results from this laboratory test may assist in the management of care for patients in a clinical or hospital setting, who present to the ED with various medical emergencies, by detecting the presence or absence of drugs from various drug classes. A positive drug screen result could help direct the treatment for the poisoned patient by utilizing antidotes, decontamination efforts and supportive care. A negative drug screen result could help rule out exposure to several drug classes.

Methods:
Standards and patient samples were prepared by adding internal standards to the aliquot prior to solid phase extraction to reduce matrix effects in urine and serum/plasma samples. Sample extracts were analyzed by LC-MS/MS using an Agilent Ultivo. The method was developed to detect >120 drugs and/or metabolites in urine and serum/plasma from the following drug classes: anticoagulants, anticonvulsants, antidepressants, antidiabetics, antihistamines, antipsychotics, benzodiazepines, cardiac medications, cough suppressants, muscle relaxants, NSAIDS, opioids, sedative hypnotics, and stimulants. The test was designed as a qualitative test with a single-point calibration curve, containing the analytes spiked at various cutoff concentrations. The assay was validated to meet regulatory requirements and the description of the method along with validation data can be found in the publication by Smith K, Johnson-Davis KL and Shahrokh K, 2023.

Results:
Retrospective data analysis was performed to evaluate the positivity rate of drug exposures in the patient population tested by ARUP Laboratories (a national reference laboratory). The age range of the patients in this population were 0 – 93 years old. There were 754 serum/plasma patient samples (Males: 396, Females: 354, Unknown: 4) and 1065 urine patient samples (Males 477, females 588). The drug classes with positivity rates >20% were stimulants, NSAIDS, anticonvulsants, opioids, antidepressants and benzodiazepines. The drug classes with positivity rates <10% were anticoagulants, antidiabetics, cough suppressants, muscle relaxants, and sedative hypnotics.

Conclusion: The multi-drug screen panel by mass spectrometry has provided clinical utility to support testing in patients who present to the emergency department to detect prescription, over-the-counter and illicit drugs.

Can we crush the pill? Case studies about the possibility of alterating solid oral dosage forms in clinics.

Dr Sara Baldelli[1], Dr Dario Cattaneo[2], Prof Matteo Cerea[3]
[1]ASST Spedali Civili Brescia, Brescia, Italy, [2]ASST Fatebenefratelli Sacco, Milano, Italy, [3]Università degli studi di Milano, Milano, Italy

Miscellaneous 2, Møterom 5, september 26, 2023, 13:00 - 14:30

Introduction:
The preferred route for drug administration is the oral route and solid oral dosage forms are the most used formulations. However, the advantages of this route are often precluded for patients with swallowing difficulties or dysphagia, very frequent in older people or children and in patients with neurological disorders, or for uncooperative or unconscious patients as those in intensive care unit. For all these cases the use of liquid dosage forms is essential.
To make available drugs that can be administered through liquid formulations, the pharmaceutical practice of pharmacies works to supply dosage forms in syrup, solution or suspension of drugs made on medical prescription. However, the raw materials of the active ingredient are not always available, and a widespread practice involves crushing tablets and opening capsules, or any other solid pharmaceutical forms available on the market, for the preparation of liquid formulations.
Alteration of solid oral pharmaceutical forms can have implications on the bioavailability of the active ingredient with consequences on the efficacy and toxicity/side effects of the therapy. The aim of our study is to show the main features that should be taken into consideration when using commercial solid drug products for the preparation of liquid composition.
Material and methods:
We present real life data about the alteration of anti-infective drug products used for the preparation of liquid compositions as alternative to solid oral dosage form. Clinical reasons for the request are also reported.
Analysis of the available features considered before crushing or splitting tablets, or suggesting chewing solid dosage forms as well as capsule opening are presented.
When possible, therapeutic drug monitoring of drug concentrations in plasma were performed with LC-MS/MS before and after the use of modified drug dosage form.
Results:
Most of the requests for alterations were for drug products containing linezolid in order to make dose adjustment. Regarding drug products for antiretroviral therapy, raltegravir and dolutegravir, crushing and chewing of tablets were necessary in case of patients with swallowing problems or of children for adapting dose regimen.
The analysis of the composition of the marketed solid oral dosage form considered the physicochemical properties of the active ingredient (mainly solubility in water), the presence of a film coating, the type and amount of excipient employed, the product information sheet and any other indication available from the literature. The behavior of the solid dosage form when in contact with aqueous media during dissolution test performed in compendial apparatus permitted to better characterize the drug product.
Therapeutic monitoring was important for evaluating the impact of the alteration of the original drug product on the pharmacokinetic profile of drugs.
Conclusions:
Real life data suggest that for specific drug product there is a critical need for alternative dosage form presentations in order to allow for dose adjustment and to enable swallowing in case of oral impairment. The literature supporting this practice is evolving, but still limited. Therapeutic monitoring is important in this particular setting as the pharmacokinetic profile of drugs is difficult to predict.

A High Throughput LC-MS/MS Method for the Determination of 52 Drugs of Abuse in Human Urine

Xu Zhang[1], Dr. Melissa Bennett[1], Ms. Hia Xia Zhou[1], Dr. David Kinniburgh[1]
[1]ACFT, University of Calgary, Calgary, Canada

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction

Substance abuse and drug overdoses have increased worldwide since the COVID-19 pandemic was declared. Harmful substances have been identified as adulterants in illicit drug material, and the risks for people who obtain drugs on the unregulated market has increased significantly due to lack of quality control and unpredictable drug contents. Toxicology/clinical laboratories need to continuously add new drugs to their analytical method and improve their throughput to cope with the challenges of increasing patient samples and new substances of abuse. Our lab developed a LC-MS/MS method with automated sample preparation for the confirmation of 52 drugs/metabolites.

Materials and Method

Using an 8 channel NIMBUS(Hamilton), 100 µL of urine and 100 µL of internal standards and IMCSzyme RT(IMCS) enzyme/buffer were mixed in a 96-well plate and hydrolyzed at room temperature for 15 min. 600 µL of methanol was then added for protein precipitation. The mixture was diluted 5 times with 0.1% acetic acid and filtered by a 0.2 µm PTFE filter plate(Pall Corporation). The samples were analyzed on an Agilent 1290 HPLC coupled with a 6470 triple quadrupole mass spectrometer operated in positive dynamic MRM mode. Separation was achieved on an Agilent Poroshell (120 EC-C18, 100x2.1mm, 2.7µm) column using gradient elution of 0.1% acetic acid and acetonitrile at 45 ºC with flow rate at 400 µL/ min.

Result

A total of 52 drugs/metabolites were analyzed in the method including 16 traditional benzodiazepines, 4 designer benzodiazepines, 15 opioids, 4 amphetamines, 4 Z-drugs, benzoylecgonine, buprenorphine, methadone, gabapentin, diphenhydramine, ritalinic acid and methylphenidate.

The method demonstrated acceptable linear range. No interferences were observed. The LOQ was 1-100 ng/mL. The accuracy ranged from 84-116%. The method demonstrated 0-15% matrix effects. No carryover was observed up to 3 times the ULOQ. Method validation results demonstrated good reproducibility with five levels of LOQ, low QC, cut-off, high QC and ULOQ control materials. Coefficients of variation (%CV) for intraday and interday precision for all controls ranged from 1.1-14%. The extraction recovery was between 87-115%. The extract was stable for 7 days.

In patient samples, some analytes can be at mg/mL levels. The ion ratio of these analytes fails at high concentrations due to overloading the MS detector. The fragmentor voltage or collision energy for these analytes were optimized to reduce overloading, while still maintaining good accuracy and precision at cut-off level.

Discussion and Conclusions

The dilute-and-shoot approach was applied for sample pre-treatment because of the wide range of chemical/physical properties of the analytes and for ease of automation. The dilution factor was optimized at 50 so that acceptable precision and accuracy was achieved for analytes with low cut-off concentrations. Adjustments made to the fragmentor and collision energy parameters for high concentration analytes has resulted in reduced time required for re-injection or up-front dilutions.

In conclusion, a high-throughput LC-MS/MS method was successfully developed for the analysis of 52 drugs of abuse in human urine. The application of this method has resulted in an increase in instrument capacity as well as a decrease in turn around time for results.

Bioanalytical LC-MS/MS method for therapeutic drug monitoring of fenfluramine in human serum and saliva

Dr Karin Kipper[1,2,3], Ms Qudsiah Munir[3], Mr Frank Quinlivan[3], Mr Anthony James[3], Dr Edgar Spencer[3], Prof Ley Sander[1]
[1]University College London, London, United Kingdom, [2]University of Tartu, Tartu, Estonia, [3]Epilepsy Society, Chalfont St Peter, United Kingdom

Miscellaneous 2, Møterom 5, september 26, 2023, 13:00 - 14:30

Introduction
Epilepsy continues to be one of the most common neurological disorders, needing new drug therapies to obtain a seizure-free life for patients. Dravet syndrome is a severe, developmental epileptic encephalopathy usually starting within the first year of life. The majority of patients remain highly resistant to the treatment with anti-seizure medications. Lennox-Gastaut syndrome is a severe form of epilepsy, usually manifesting before the age of 4 years. Fenfluramine acts as a potent releaser reuptake inhibitor for serotonin. It was initially introduced as an anorectic following the market withdrawal in 1997 due to cardiopulmonary side effects. Fenfluramine However, in lower doses, fenfluramine as an add-on therapy is promising in reducing seizures or providing seizure freedom for patients with Dravet syndrome and Lennox-Gastaut syndrome.
Therapeutic drug monitoring (TDM) of pharmacokinetically variable anti-seizure medications helps to guide dose adjustment and tailor a bespoke approach for people with epilepsy. Saliva can act as an alternative matrix for blood to TDM of anti-seizure medications and can be especially useful for paediatric patients. Hereby, we demonstrate fully validated bioanalytical assays for fenfluramine and its active metabolite norfenfluramine in human serum and saliva, allowing to guide dose optimisation. To the best of our knowledge, this is the first-ever salivary fenfluramine assay.

Materials and Methods
Assays are using minimal serum and saliva volumes of 50 µL. Samples preparation included protein precipitation with acetonitrile. The separation of fenfluramine and norfenfluramine from matrix components with a short retention time of 1.6-1.7 min was obtained using a C18 column and 0.01% formic acid in water and methanol gradient elution. Fenfluramine and norfenfluramine were detected in MRM mode with a triple-quadrupole mass spectrometer.

Results
The bioanalytical LC-MS/MS assay in serum demonstrated excellent intra- and inter-day accuracy (<4%) and precision (<4%) for fenfluramine and intra- and inter-day accuracy (<4%) and precision (<7%) for norfenfluramine in serum and saliva. Assays were inear (r2>0.99) over the concentration range of 5-750 ng/mL for fenfluramine and 5-800 ng/mL for norfenfuramine. The lowest limit of quantification in human serum and saliva was 5 ng/mL with intra- and inter-day accuracy <14% and precision <6%. Good selectivity was achieved in the presence of other anti-seizure medications and in various matrices. No significant matrix effects were observed. The stability of both analytes was excellent in serum and saliva after storage of samples at ambient temperature and fridge for 10 weeks.
Fenfluramine trough levels in patient serum samples ranged from 83 to 259 ng/mL and norfenfluramine from 6 to 7 ng/mL following 2.2mg and 6.6mg doses.

Discussion and Conclusions
The first-ever validated salivary LC–MS/MS assay for quantification of fenfluramine and norfenfluramine is reported. The stability of both analytes was suitable to support remote sample collection and transportation of samples to the laboratory using postal services. Assay was successfully applied for TDM of fenfluramine in paediatric patients' serum samples. There is very little data on therapeutic reference ranges for fenfluramine and norfenfluramine in treating epilepsy.

Salivary TDM could be beneficial as an alternative non-invasive sample collection for paediatric patients.

Pharmacokinetic analysis of carboplatin in Japanese patients with Stage I seminoma after high orchidectomy

Dr. Tomoya Shimokata[1], Dr. Kazuna Matsuo[1], Dr. Yoshihisa Matsukawa[1], Dr. Masashi Kato[1], Dr. Yuichi Ando[1]
[1]Nagoya University Hospital, Nagoya, Japan

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction: Germ cell tumors are the most common solid tumors in males aged 15–35 years. Surveillance, prophylactic radiation therapy, and adjuvant chemotherapy with carboplatin are the treatment options for patients with Stage I seminomas, after high orchidectomy. Carboplatin dosage is determined using the Calvert formula, which is carboplatin dose (mg) = target area under the concentration versus time curve (AUC)(mg/mL min)×[glomerular filtration rate (GFR)(mL/min)+25]. The dose is calculated using a target AUC of 7, but a higher recurrence rate is reported when the actual AUC is less than 7 (5-year relapse-free rate: ≥ AUC 7; 96.1% vs < AUC 7; 92.5%); thus, under-dosage should be avoided to the greatest extent possible. Although the renal function is generally good because most seminoma patients are young, the validity of the Calvert formula in Japanese patients with good renal function has not been confirmed; this formula's validity in this population was evaluated prospectively.
Materials and Methods: This study included Japanese patients with histologically confirmed Stage I postoperative seminoma, who were receiving carboplatin as adjuvant therapy. Carboplatin dosage was calculated using the Calvert formula, with GFR measured by inulin clearance and target AUC 7; the dose was given as a 1-h intravenous infusion with monotherapy. Heparinized blood samples were procured before the start, at the end of the infusion, and 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h after the end of infusion for pharmacokinetic analysis. The unbound platinum level was determined using atomic absorption spectrophotometry, and the pharmacokinetics of carboplatin were studied using a non-compartment model by WinNonlin. We validated the Calvert formula in this population by assessing carboplatin clearance using the Calvert formula and comparing it to measured carboplatin clearance.
Results: This study included ten patients with Stage I seminoma after high orchidectomy. The patients' median age was 42 (range 25–59), their serum creatinine level was 0.80 mg/dL (range 0.66–1.11), and their inulin clearance was 95.6 mL/min (range 68.8–108.6). The mean-measured carboplatin AUC was 6.65±0.57, and the median-observed carboplatin clearance was 124.5 mL/min (93.8–156.4). The Calvert formula underestimated carboplatin clearance, resulting in a −5.0% mean prediction error (MPE) and a 9.6% root mean squared error. Patients with high GFR tended to underestimate carboplatin clearance (MPE: GFR≥100 mL/min; −5.9% vs GFR<100 mL/min; −4.4%).
Discussions and Conclusions: The Calvert formula was validated in Japanese patients with Stage I seminoma after high orchidectomy. When the dosage was calculated using the Calvert formula, the actual AUC values of carboplatin were slightly lower than the target value 7, indicating a tendency to under-dose. Although the Calvert formula's estimation of carboplatin clearance was clinically acceptable and unbiased, it was still underestimated in Japanese patients, particularly those with GFR greater than 100 mL/min. Therefore, more research is needed to determine the carboplatin dosage in this population.

Comparison of pharmacokinetic profiles of once-daily 3-hour and 6-hour infusion of Busulfan using population pharmacokinetic model in pediatric patients

MD Sungyeun Bae[1], MD, PhD In-Jin Jang[1], MD, PhD Jae-Yong Chung[2], PhD Su-Jin Rhee[3]
[1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, South Korea, [2]Department of Clinical Pharmacology and Therapeutics, Seoul National University Bundang Hospital, Seongnam, South Korea, [3]Department of Pharmacy, Wonkwang University College of Pharmacy, Iksan, South Korea

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction

Busulfan is an alkylating agent used in advance of hematopoietic stem cell transplantation (HSCT). While FDA and EMA recommends 2-hour infusion every 6 hours for 4 days, several once-daily regimens have been proposed with the help of pharmacokinetic (PK) modeling. This study aimed to compare the PK profiles of once-daily 3-hour and 6-hour infusion of Busulfan using population PK model in pediatric patients.

Material and Methods

Busulfan concentrations were collected from therapeutic drug monitoring data of pediatric patients who underwent HSCT in Seoul National University Children's Hospital, Seoul from 2009 to 2020. Busulfan was administered either over three or six hours once daily and PK blood samples were collected at 0, 1, 2, and 4 hours after the end of infusion. A population PK model was developed with NONMEM (version 7.4.4, ICON Development Solutions, Ellicott City, MD, USA) using first-order conditional estimation method with interaction (FOCE-I). Area under the curve (AUC) of Busulfan was calculated as dose divided by clearance. Age, height, weight, body surface area (BSA), total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), serum creatinine, and sex were explored during covariate analysis.

Results

A total of 6989 concentration data were obtained from 413 pediatric patients (137 and 276 patients after 3-hour and 6-hour infusion, respectively). The age, weight, height, and BSA were similar between the regimen. A one-compartment linear elimination model with proportional residual variability adequately described the observed concentration–time profiles of Busulfan. BSA, AST, and dosing day were found to be the significant covariates for clearance and BSA with age for the volume of distribution. While the covariate-adjusted clearance and volume of distribution were similar between the two regimen, the clearance in the 3-hour infusion group was more influenced by dosing day, and decreased 5 ~ 13% compared to that of the first day. The mean AUC and dose divided by BSA per day were 18998.5 ng/mL*h and 107.8 mg/m2 for the 3-hour infusion group and 18642.7 ng/mL*h and 101.6 mg/m2 for the 6-hour infusion group, respectively.

Discussions and Conclusion

The overall PK profiles of Busulfan was similar between 3-hour and 6-hour once-daily regimen. The difference in overall exposure between the two groups was also negligible. Nevertheless, reduction in Busulfan clearance was observed in the patients with moderate AST and/or ALT elevation in the 3-hour infusion group. The shorter infusion time and higher maximum concentration of Busulfan might have led to liver damage. Other clinical markers such as occurrence rate of adverse events or efficacy related to Busulfan can be compared between these two regimen in the future studies.

Can laboratorians interpret the tests they perform? Lessons from pain management proficiency testing.

Dr Christine Snozek[1]
[1]Mayo Clinic Arizona, Phoenix, United States

Toxicology -clinical and environmental, Sal C, september 26, 2023, 13:00 - 14:30

Despite the potential clinical importance of pain management and drug of misuse testing, several studies have shown that providers in various specialties struggle with drug test interpretation. Clinical and laboratory guidelines recommend providers contact the testing laboratory for support when needed, yet there is little published literature to demonstrate laboratorian competence in interpreting drug test results. The College of American Pathologists (CAP) Drug Monitoring for Pain Management (DMPM) proficiency testing (PT) survey includes a real-world, case-based 'dry' interpretive challenge with each PT event. Each case scenario presents a patient scenario including a list of prescribed and non-prescribed medications and relevant drug test results. Laboratories are asked to respond whether the test results given are consistent or inconsistent with the prescribed medications in the case description.

Dry challenge results were reviewed from 2012-2022 to evaluate participants' interpretive knowledge. In 15 of 22 challenges, >90% of participating laboratories correctly interpreted the drug test results in relationship to the prescribed medication list. Several themes were identified in the 7 case scenarios with <90% correct participant responses, including interpretation of false positive screening results and recognition of minor opiate metabolism. Laboratories performed better on challenges presenting results that were inconsistent with prescribed medications; all of these involved detection of controlled substances and/or recreational drugs not in the patient's medication list. One challenge required participants to recognize high concentrations of the prescribed medication in the absence of metabolites as suggestive of simulated compliance.

The DMPM survey challenged participants with a variety of real-world scenarios; all were cases that clinicians and laboratorians in a true patient care setting might face routinely. Overall, participants performed extremely well, supporting guideline recommendations to consult the testing laboratory to address troubling questions. However, some themes for additional targeted education of testing laboratory staff were identified, particularly to address complex interpretive scenarios such as minor metabolism and simulated compliance. This presentation will discuss these themes and other potential opportunities for future educational efforts within the laboratory medicine community.

Investigating the effect of tacrolimus exposure on the acute rejection reaction after pediatric liver transplantation using population pharmacokinetic analysis

Yuta Yokoyama[1,2], Momoka Murakami[1], Jumpei Saito[3], Seiichi Shimizu[4], Hajime Uchida[4], Akinari Fukuda[4], Seisuke Sakamoto[4], Aya Jibiki[2], Hitoshi Kawazoe[1,2], Mureo Kasahara[4], Akimasa Yamatani[3], Sayo Suzuki[1,2], Tomonori Nakamura[1,2]

[1]Division of Pharmaceutical Care Sciences, Keio University Graduate School of Pharmaceutical Sciences, Tokyo, Japan, [2]Division of Pharmaceutical Care Sciences, Center for Social Pharmacy and Pharmaceutical Care Sciences, Keio University Faculty of Pharmacy, Tokyo, Japan, [3]Department of Pharmacy, National Center for Child Health and Development, Tokyo, Japan, [4]Organ Transplantation Center, National Center for Child Health and Development, Tokyo, Japan

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction: Tacrolimus (TAC) is a calcineurin-inhibiting immunosuppressive drug used to prevent rejection reactions after liver transplantation. In pediatric liver transplantation, interindividual variability in TAC blood concentrations is associated with acute and late-onset rejection; however, the association between TAC area under the blood concentration-time curve (AUC) and rejection in the acute postoperative period has not been investigated. In this study, the AUC of TAC was calculated using population pharmacokinetic (PPK) analysis in pediatric patients after liver transplantation and the effect of TAC exposure on the rejection reaction in the early postoperative period was investigated.

Materials and Methods: Blood concentrations and clinical information including rejection status were obtained from the medical records of pediatric patients who underwent liver transplantation and received TAC between April 2018 and November 2021 at the National Center for Child Health and Development. Rejection reaction was determined from liver biopsy diagnosis or administration of other immunosuppressive agents. A PPK model was developed using Phoenix® NLME™ 8.3 software. Clearance (CL) for each patient was estimated by PPK analysis using the trough concentration before TAC administration, and the AUC was calculated. This study was approved by the ethics committees of the National Center for Child Health and Development (approval number: 2021-224) and Keio University Faculty of Pharmacy (approval number: 220128-1).

Results: PPK analysis was performed using trough concentrations (n = 1661, 10.4 [0.5–36.6] ng/mL) from 66 post-liver transplant pediatric patients (median age (range): 11 [4–137] months). A one-compartment model was used, incorporating the concomitant use of a proton pump inhibitor, AST, total bilirubin, body weight (at transplant), serum albumin levels as covariates for CL, and body weight as covariates for the volume of distribution. The AUC0–12 h (190 ± 87 ng·h/mL) was calculated from the CL (3.8 L/h, CV%: 6.66) estimated using the final model. No correlation between trough concentrations and the AUC0–12 h of TAC during the first 7 days after transplantation was identified ($r = 0.28$). The variability of AUC0–12 h during the first 7 days after transplantation was significantly higher in the rejection group than that in the non-rejection group (median: 275 [range: 156–675] ng·h/mL vs. 260 [120–485] ng·h/mL, ($p < 0.05$)). The Kaplan–Meier method, which was divided into two groups based on the cutoff value (273 ng·h/mL), showed a significant association ($p = 0.039$) in the group with AUC variability > 273 ng·h/mL between variability and rejection reaction in the first 30 days after transplantation, with significantly greater trough concentration variability, CV, and variability of concentration/dose (C/D) ($p = 0.006$, $p < 0.001$, and $p = 0.003$, respectively).

Discussion and Conclusions: No correlation between trough concentrations and the AUC of tacrolimus was identified, similar to previous reports on pediatric transplantation. AUC variability was associated with trough concentrations and C/D, suggesting that monitoring these is important for predicting acute rejection reactions. In conclusion, PPK modeling in pediatric patients after liver transplantation suggests that intra-individual variability of the AUC in the early postoperative period affects the acute rejection reaction.

Comparison of an ELISA and a UPLC-MS/MS method for quantification of pembrolizumab in human plasma

Msc Fenna de Vries[1,2], Msc Leila-Sophie Otten[2], PhD Rob ter Hein[2], PhD Floris Loeff[3], Msc Lindsey te Brake[2], PhD Eric Franssen[1]
[1]Department of Pharmacy, OLVG, , Amsterdam, The Netherlands, [2]Department of Pharmacy, Radboudumc, Nijmegen, The Netherlands, [3]Sanquin Diagnostic Services, Amsterdam, The Netherlands

Miscellaneous 1, Møterom 2, september 26, 2023, 13:00 - 14:30

Introduction
For clinical pharmacological research purposes of the anti-cancer, PD-1 inhibitor pembrolizumab, reliable quantification in biological matrices is of utmost importance. However, even in validated quantification methods, differences are often inevitable. (1,2) These differences should be identified and quantified to perform mandatory corrections for these differences in clinical pharmacological research wherein multiple quantification methods are used. Therefore, we aimed to determine the agreement between an enzyme-linked immunosorbent assay (ELISA) method and an ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method of pembrolizumab.

Materials and Methods
In the context of an observational study, 439 blood samples were collected from stage IV non-small cell lung cancer patients with pembrolizumab treatment at OLVG. Pembrolizumab quantification was performed using an, per FDA guideline on bioanalytical method validated, ELISA method (lower limit of quantification (LLOQ): 0.2 µg/mL) by Sanquin Health Solutions. A selection of 30 samples with ELISA concentrations of 2.51 µg/mL to 111.00 µg/mL (median: 13.95 µg/mL) was also quantified by a, per EMA guidelines validated, UPLC-MS/MS method (LLOQ: 2 µg/mL) by Radboudumc.
Statistical analyses were performed using RStudio and the mcr- and SimplyAgree packages. (3–5) The line of best fit between both methods and Pearson's correlation coefficient (p) were calculated using linear regression. The agreement between the reference UPLC-MS/MS method and the alternative ELISA method was assessed using a Bland-Altman plot (mean of ELISA and UPLC-MS/MS versus ELISA-UPLC-MS/MS. The mean bias and mean relative bias between both methods were described, the 95% limits of agreement (LoA) (average difference ± 1.96 standard deviations of the difference) were calculated and the presence of a proportional bias and normality of the residuals was tested using the Test for Linear Bias and the Shapiro-Wilk test, respectively.
Results
Of the thirty samples, one sample was not successfully analysed by both methods due to a pre-processing dilution error and insufficient sample volume for a redo. The UPLC-MS/MS method quantified concentrations ranging from 2.65 µg/mL to 98.84 µg/mL (median: 13.50 µg/mL). Linear regression analysis revealed a p of .978, an intercept of -3.58 µg/mL (95% CI: -7.39 to .23), and a slope of 1.24 (95% CI: 1.13 to 1.34). The Bland-Altman plot displayed a proportional bias (p = 1.178*10-11) and non-normally distributed residuals (p = 8.708*10-5). The mean bias was 2.61 µg/mL with LoAs of 15.93 µg/mL and 21.16 µg/mL. Three samples in the higher regions (70 µg/mL to 111 µg/mL) fell above the upper LoA. The mean relative bias was -2.2%, with LoAs of -57.28% and 52.88%. No proportional bias was present (p = 0.81), and the residuals were distributed normally (p = 0.37). Nonetheless, one sample (9.38 µg/mL by UPCL-MS/MS versus 3.05 µg/mL by ELISA) fell beneath the lower LoA.

Discussion and Conclusion
The method comparison showed a strong positive correlation between both methods. Furthermore, the comparison of the relative difference values showed a better distribution and lesser bias than the absolute difference values. Our results show the necessity of bioanalytical method comparison in

clinical pharmacological research of PD(L)-1 inhibitors to facilitate the comparison of quantitative results.

Distribution of citalopram enantiomers following medication with racemic citalopram - a naturalistic Therapeutic Drug Monitoring study

Md Ketil Arne Espnes[1], MD Arne Hønnås[1], PhD Olav Spigset[1,2]
[1]St. Olavs hospital, Trondheim University Hospital, Trondheim, Norway, [2]Department of Clinical and Molecular Medicine (IKOM), Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

Psychiatry, Møterom 4, september 25, 2023, 13:00 - 14:30

Introduction
For several decades, citalopram, which consists of a racemate (a 50/50 mix) of the enantiomers S-citalopram and R-citalopram, has been used in the treatment of depression and other mental disorders. When escitalopram, which consists of the pure enantiomer S-citalopram, was introduced as a separate medication and gradually replaced racemic citalopram in common use, there were prolonged academic discussions on the reasons why the dose needed for escitalopram was less than half of the dose of racemic citalopram to achieve the same antidepressant effect, apparently showing higher efficacy. Since a racemic drug contains equal amounts of S- and R-enantiomers when administered, simple pharmacokinetic models would assume that 10 mg of escitalopram would be needed to yield the same effect as 20 mg of racemic citalopram.

Materials and methods
At the Department of Clinical Pharmacology at St. Olav's hospital, the University hospital of Trondheim, Norway, we changed our routine service in February 2017 to analyze the S- and R-enantiomers of citalopram separately, thus being able to distinguish between patients using escitalopram and racemic citalopram solely based on the laboratory result.
The results from routine samples analyzed at our laboratory were retrieved from our in-house database. We examined the samples where we found both S-citalopram and R-citalopram (n= 520 samples), in order to establish the standard percentage of the two enantiomers in samples obtained at steady state conditions. In addition, we investigated whether these percentages change with gender, age or the dose of citalopram.
Parameters were estimated using the method of restricted maximum likelihood, employing the Stata version 17 menl procedure for nonlinear mixed effects.

Results
From the 520 samples obtained we dismissed samples with missing information according to a list of predefined criteria. This procedure resulted in 305 samples from 237 individuals, which entered in the statistical analysis.
We found the mean percentage of S-citalopram (% S-cit) to be 32.0 % (95 % CI: 27.8 – 36.3 %). There was no dose-related difference in % S-cit (p= 0.644), a non-significant tendency towards higher % S-cit in males than in females (p= 0.189). We found a statistically significant rise in % S-cit with increasing age (p= 0.049).

Discussions and conclusions
A mean % S-cit of 32 % is consistent with earlier findings (1, 2, 3). This can been explained with the difference in enzyme metabolism and affinity to the metabolizing enzymes between the R- and the S-enatiomers, leading to a lower clearance of the R-enantiomer.
The dose-dependent variation shown by Tanum et al. (1), can be understood inversely: With a low % S-cit (the active enantiomer) the dosage was increased to achieve the desired effect. Then, the patients with the highest doses will have the lowest % S-cit.
The trend towards higher % S-cit in men and the increasing % S-cit with increasing age in our study is most likely due to a difference in clearance between the enantiomers (4), probably because of a

variation in the activity of metabolic enzymes between genders, and changes in the enzyme activity with increasing age.

Physiologically-based pharmacokinetic modeling and simulation of fentanyl for treatment optimization in neonates

Dr. Kazuhiro Yamamoto[1], Dr. Walaa Yousef Bassyouni Mahdy[1,2], Ms. Mari Hashimoto[1], Ms. Mai Hasegawa[3], Dr. Ruka Nakasone[4], Dr. Kazumichi Fujioka[4], Dr. Kotaro Itohara[1], Dr. Yumi Kitahiro[1], Dr. Tomohiro Omura[1], Prof. Ikuko Yano[1]

[1]Department of Pharmacy, Kobe University Hospital, Kobe, Japan, [2]Department of Forensic Medicine and Clinical Toxicology, Assiut University, Graduate School of Medicine, Assiut, Egypt, [3]Education and Research Center for Clinical Pharmacy, Kobe Pharmaceutical University, Kobe, Japan, [4]Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Background: Fentanyl is used for sedation during endotracheal intubation and mechanical ventilation in neonates with immature lung function. The serum fentanyl concentration relating to adverse reactions and clinical effectiveness remains unclear in neonates. This study aimed to evaluate the association between the simulated serum fentanyl concentration and pharmacological reactions caused by fentanyl using physiologically-based pharmacokinetic (PBPK) model.

Methods: Neonatal patients who received a continuous infusion of fentanyl during endotracheal intubation and mechanical ventilation were included. The assessable adverse reactions of fentanyl were defined as hypotension or oxygen desaturation. The clinical effectiveness was assessed as wakefulness defined as the time of extubation after the termination of the fentanyl therapy. PBPK modeling and simulation were performed using Simcyp Population-based ADME Simulator version 22. The fentanyl compound model was developed based on physicochemical and pharmacokinetic parameters reported in the literature. The model was validated using the reported values from clinical studies and applied to our neonatal patients with the “virtual twin” approach. Effects of neonatal maturation on the pharmacokinetic parameters of fentanyl were evaluated by the simulation study.

Results: In this study, 47 neonatal patients with 115 serum fentanyl concentrations were applied in the PBPK simulation. The mean percentage error and root-mean-square percentage error of all fentanyl concentrations simulated by PBPK model for our data from 41 neonates whose measured fentanyl concentrations were 5.9 ± 21% and 48.5%, respectively. Hypotension and oxygen desaturation were observed in 21 neonates (44.7%) and 26 neonates (55.3%), respectively. There was no significant difference between the simulated concentration at the incidence of hypotension and the simulated maximum concentration in patients without hypotension. Similar results were observed for oxygen desaturation. The median simulated concentration at wakefulness after the termination of the fentanyl therapy was 0.52 (IQR: 0.24–0.95) ng/mL. PBPK simulation revealed that the neonatal clearance of fentanyl increased 2.67-fold from 25 to 40 gestational weeks and the contribution of CYP3A4-mediated clearance to total clearance according to the gestational age progressed.

Conclusion: Serum fentanyl concentrations under 0.52 ng/mL were related to wakefulness after the termination of the fentanyl therapy, but the safety threshold was not clarified. Changes of activity and transition of fentanyl metabolic pathway according to the gestational age might be considered in individual dosage adjustment.

A biological pharmacology network to secure the risk of drug-drug interaction with nirmatrelvir/ritonavir

Dr Florian Lemaitre[1], Dr Lidvine Boland[2], Dr Camille Tron[1], Dr Anne-Lise Ruelland[3], Pr Véronique Lelong-Boulouard[4], Dr Sarah Baklouti[5], Dr Françoise Goirand[6], Dr Nicolas Gambier[7], Dr Christelle Boglione-Kerrien[1], Dr Bénédicte Franck[1], Dr Sébastien Lalanne[1], Pr Arnaud Devresse[2], Dr Sébastien Briol[2], Dr Julien De Greef[2], Pr Vincent Haufroid[2], Dr Marie-clémence Verdier[1]
[1]Rennes University Hospital, Rennes, France, [2]Cliniques Universitaires Saint-Luc, UC Louvain, Brussels, Belgium, [3]CHU Nantes, Nantes, France, [4]Centre Hospitalo-Universitaire Caen-Normandie, Caen, France, [5]IFB, Hôpital Purpan, Toulouse, France, [6]CHU de Dijon, Dijon, France, [7]Université de Lorraine, CNRS, IMoPA, Nancy, France

Miscellaneous 2, Møterom 5, september 26, 2023, 13:00 - 14:30

Introduction:
Nirmatrelvir/ritonavir (Paxlovid©) is a protease inhibitor antiviral drug indicated in the treatment of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections in high-risk patients for a severe disease. Unfortunately, ritonavir, used to boost nirmatrelvir pharmacokinetics, can also inhibit or induce the metabolism of other co-administered drugs substrates. This may lead to a subsequent risk of adverse drug reaction. In this study, we aimed at describing the expert advices provided by the biological pharmacology network of the SFPT (i.e the therapeutic drug monitoring specialists working in the laboratories of pharmacology departments in France/Belgium).

Material and methods:
From February to August 2022, we collected all specialized advices provided by 7 pharmacology departments participating in the SFPT biological pharmacology network (Brussels in Belgium, Caen, Dijon, Nantes, Nancy, Rennes and Toulouse in France). We collected the following data: patient's age, date of nirmatrelvir/ritonavir initiation, clinical department requiring the expert advices, patient's treatments, and advice provided. These advices have been provided using SmPCs, DDI and cohort studies retrieved in medical databases and the SFPT guidelines.

Results:
One hundred and six expert advices on 753 drugs were provided during the seven months of data collection. Patients originated from a transplantation department in 65% of the cases. Cardiac drugs (32%), immunosuppressive drugs (27%) and endocrine drugs (21%) were the most common requests. Advices were: treatment continuation, treatment discontinuation during the antiviral course, dosage adjustment and treatment switch in 59%, 28%, 11%, 1.6% of the cases, respectively. Only 2 advices (0.3%) were nirmatrelvir/ritonavir contra-indications. Drug monitoring was proposed in 10% of drugs.

Conclusion:
Expert advices provided by the biological pharmacology network of the SFPT allows securing the combination of nirmatrelvir/ritonavir with other concomitant drugs. Most of eligible patients to the antiviral drug can benefit from it despite the risk of drug-drug interaction.

Mycophenolic acid therapeutic drug monitoring: A clinical practice guideline

Shuang Liu[1], Mr. Zaiwei Song
[1]Peking University Third Hospital, Beijing, China

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Mycophenolic acid therapeutic drug monitoring: A clinical practice guideline

Abstract
Background Mycophenolic acid (MPA) drugs are widely accepted as the first-line immunosuppressants in the maintenance therapy of organ transplantation, due to their significant clinical significance. However, the significant inter- and intra-individual variability in MPA metabolism makes it challenging to personalize and rationalize its use fully. Conducting therapeutic drug monitoring (TDM) of MPA can help to overcome this challenge, leading to better patient outcomes. This study aims to develop an MPA TDM guideline based on an evidence-based approach to provide guidance for the rational application of MPA drugs in clinical settings.
Method To develop the guideline plan, the latest guidelines from the Institute of Medicine (IOM) in the United States and the basic principles and methods developed based on World Health Organization (WHO) guidelines were used. The Delphi method was used to determine the clinical questions and outcome indicators included in the guideline. By conducting a systematic review, evidence-based evidence for the clinical issues in the guideline was established, combined with Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence quality evaluation, expert opinions, and patient values and beliefs. After undergoing external experts review, the final guideline recommendations were formed.
Results The evidence-based MPA TDM guideline (IPGRP-2020CN099) includes four parts and 16 recommendations, involving target populations, monitoring strategies, dosage regimen, and influencing factors. The guideline further clarifies the definition of high-risk populations for MPA TDM, the timing of TDM, comparison of AUC and trough concentration, target concentration ranges, monitoring frequency, and comparison of analytical methods. In addition, the guideline also provides evidence-based recommendations for different formulations of MPA drugs, initial dosage regimen, special populations, PK-informed dosing, body weight factors, pharmacogenetics and drug-drug interactions.
Conclusions The MPA TDM evidence-based guideline provides comprehensive and practical guidance for solid organ transplant recipients receiving MPA drug treatment, promoting the standardization and standardization of MPA TDM and improving the treatment effectiveness and safety of transplant recipients. When conducting MPA TDM, it is recommended to comprehensively evaluate patient individualized characteristics and adjust the dosage according to the patient's drug exposure and clinical response. This guideline will also contribute to the further development of TDM and personalized drug therapy for other drugs in the future.
Keywords guideline, mycophenolic acid, therapeutic drug monitoring, GRADE

Optical parameters of leukemia-related chemotherapeutic drugs

Ms. Dóra Bereczki[1,2,3], Ms. Ines Lidia Haffaressas[3], Dr. Péter Fürjes[1], Dr. András Füredi[3]
[1]Microsystems Laboratory, Institute of Technical Physics and Materials Science, Centre for Energy Research, Budapest, Hungary, [2]Doctoral School on Materials Sciences and Technologies, Óbuda University, Budapest, Hungary, [3]Institute of Enzymology, Research Centre for Natural Sciences, Budapest, Hungary

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Chemotherapy is the most frequently used non-surgical method in clinical practice in cancer treatment to depress the growing, proliferation, or spreading of cancer cells. Detection of the anti-cancer drugs in patients' blood or standard cell culture media is the fundamental step forward in personal treatments or in vitro drug tests in Organ-on-Chip devices. Besides the golden standard mass spectrometry, optical spectroscopy has to be considered as a potential analytical method, although there is no extensively accessible database of the spectral characteristics of the widely applied chemotherapeutic drug compounds. There are some well-known examples of anticancer molecules with strong fluorescence like the anthracycline family, however systemic screening for fluorescent drugs used in oncology was never done before. In this work, our aim was to determine the spectral properties of a wide library of commercially available chemotherapeutic drugs used to treat leukemia and identify the molecules with fluorescent characteristics.

The compounds were characterized by using Tecan Spark Plate Reader to determine their spectral absorbance and fluorescence emission. A UV-transparent 96-microplate was applied for the measurements in the UV-VIS spectral range. The drugs were dissolved in dimethyl sulfoxide (DMSO) buffer solution and clinically relevant concentration was set. First, the absorption spectra were recorded to find the optimal fluorescence excitation wavelength range and then the fluorescence emission spectra were analyzed. Based on these results, the relevant chemotherapeutics having strong fluorescence emission were selected and measured in a concentration-dependent manner in Dulbecco's Modified Eagle Medium, fetal bovine serum, and spiked whole blood, respectively.

Surprisingly, 20 out of 90 molecules were found to show intense fluorescence emission in the visible spectral range, which could be the potential characteristics to be applied for the selective detection of these molecules even in biological samples. By exploiting the properties of these compounds, this demonstrated optical method could be appropriate for monitoring blood plasma drug levels or continuous in-situ concentration measurements for in vitro experiments.

The spectral properties of various chemotherapeutic drugs were characterized to establish a detailed database. Recording and cataloging the spectral parameters of these anti-cancer drug molecules are crucial to exploit their fluorescent fingerprints for specific detection in a biological environment. Based on the results, at least 20 % of all chemotherapeutic drug molecules in our screened library showed intense fluorescence in the VIS region, and making it possible to detect these agents in complex biological matrices such as blood plasma or even in whole blood. Accordingly, in the case of these drug molecules, their blood plasma level could be monitored selectively and specifically or their concentration could be measured in vitro by non-contact optical detection either in microfluidic or in Organ-on-Chip systems.

Monitoring of antiarrhythmic drugs by HPLC-UV – new life for an old method

Dr Paweł K. Kunicki[1], MPharm Jakub Meszka, MPharm Wioleta Opieka
[1]Medical University of Warsaw, Department of Drug Chemistry, Warsaw, Polska

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction: For over 25 years, a simple HPLC-UV method (Kunicki P.K. et al., J. Liq. Chrom. Rel. Technol. 1996; 19: 1169-1181) has been successfully used in the hospital laboratory for therapeutic drug monitoring (TDM) of antiarrhythmic agents in patients' serum samples. Recently, the methodology needed to be modified due to the unavailability of the compounds originally used as internal standards (ISs) i.e. L8040 for amiodarone (AD) and LU41616 for propafenone (PPF). The aim of the work was to select new, appropriate ISs and to change the extraction mode from manual to automatic.
Methods: A simple isocratic HPLC-UV system (Spectra Physics) with a manual injector (50 µL loop) was applied. The separation was performed at ambient temperature on Supelcosil LC-CN column (150x4.6 mm, 5 µm). Two analytical procedures (A and B) were used: (A) for AD and desethylamiodarone (DEAD), and (B) for PPF, 5-hydroxypropafenone (5OHPPF), N-depropylpropafenone (NDPPF) and mexiletine (MEX). The mobile phase for (A) was a mixture of: CH_3OH:CH_3CN:H_2O:0.5M KH_2PO_4:H_3PO_4 (400:200:388:12:0.2, v/v). Slightly acidified serum sample was extracted with hexane and the analytes were detected at 240 nm. The mobile phase for (B) was a mixture of: CH_3CN:H_2O:0.5M KH_2PO_4:H_3PO_4 (620:370:10:0.2, v/v). Alkalized serum sample was extracted with diisopropyl ether, then back extracted into 0.01N HCl and finally the analytes were detected at 210 nm.
Results: (A): Out of two: tamoxifen and bepridil (BEP) analytically appropriate ISs, BEP was selected due to its current disuse as a drug. Manual extraction has been replaced by automatic using a rotary mixer (Reax 2, Heidolph), yielding 84-88%, 45-55% and 86-92% for AD, DEAD and BEP, respectively. The method has been validated in the range of 20-4000 ng/mL. For intraassay, the mean inaccuracy ranged from -4.71% to +3.87% for AD and from -8.64% to +5.50% for DEAD and imprecision ranged from 0.86% to 6.00% for AD and from 0.83% to 10.87% for DEAD. For interassay, the inaccuracy was from -3.10% to +3.83% for AD and from +2.76% to +18.01% for DEAD; the imprecision ranged from 0.98% to 6.74% for AD and from 6.29% to 13.11% for DEAD.
(B): Among the potential ISs, gallopamil (currently unregistered) was selected due to its adequate elution and extraction yield of 76%. The automatic extraction resulted in average recoveries of 72%, 68%, 68% and 84% for PPF, 5OHPPF, NDPPF and MEX, respectively. The method was calibrated in the ranges: 10-4000 ng/mL for PPF, 10-500 ng/mL for 5OHPPF and for NDPPF, and 20-4000 ng/mL for MEX. The intraassay / interassay imprecision was found: <10.00% / <10.62% for PPF, <8.68% / <6.88% for 5OHPPF, <8.68% / <9.16% for NDPPF and <8.21% / <7.28% for MEX. The intraassay / interassay inaccuracy was less than: 2.08% / 17.87% for PPF, 6.26% / 7.21% for 5OHPPF, 12.74% / 14.64% for NDPPF, and 10.15% / 3.50% for MEX.
Conclusions: The validation parameters met the requirements, proving that the modified method can be successfully used for TDM. It can be recommended for laboratories equipped with basic HPLC apparatus as an economical alternative to the LC-MS/MS technique.

Inhibitory effects of CYP3A4 inhibitors voriconazole, itraconazole, and fluconazole on the pharmacokinetic profile of ceritinib in rats revealed by HPLC-MS/MS analysis

Mr. Yutao Lou[1], Dr. Hui Qin[1], Dr. Feifeng Song[1], Yiwen Zhang[1,2]
[1]Clinical Pharmacy Center, Department of Pharmacy, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, China, [2]Key Laboratory of Endocrine Gland Diseases of Zhejiang Province, Hangzhou, China

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction: Ceritinib can be used to treat patients with non-small cell lung cancer. Triazole antifungals are therapeutic choices for patients with cancer to reduce the risk of opportunistic fungal infections. In this study, we investigated whether three triazole antifungal CYP3A4 inhibitors (voriconazole, itraconazole, and fluconazole) affect the pharmacokinetics of ceritinib in rats.
Methods: Ceritinib was orally administered to rats, either by itself or in combination with voriconazole, itraconazole, or fluconazole, and its pharmacokinetic parameters across treatments were compared. The plasma concentration of ceritinib was determined using a validated HPLC–MS/MS method.
Results: Compared to the control group, co-administration with voriconazole and fluconazole increased the Cmax of ceritinib by 14.71% and 3.13%, respectively, and increased the AUC0-t to 1.22- and 1.29- fold, respectively. Although the Cmax and AUC0-t upon co-administration were higher than those resulting from ceritinib alone, there was no significant difference in all parameters. However, when ceritinib was administered in combination with itraconazole, the Cmax and AUC0-t of ceritinib significantly increased by 1.49- and 1.91-fold, respectively. In contrast, the Vz/F and CL/F significantly decreased by 33.39% and 51.42%, respectively, compared to those yielded by ceritinib administration alone. These results imply that among the CYP3A4 inhibitors evaluated in this study, only itraconazole contributed to increased systemic exposure to ceritinib and decreased its clearance. Therefore, itraconazole had a greater inhibitory effect on the absorption and distribution of ceritinib in rats than voriconazole or fluconazole.
Conclusions: This study showed that co-administration with itraconazole had a significant effect on the pharmacokinetics of ceritinib, whereas the co-administration of ceritinib with voriconazole or fluconazole had no effect. Dose adjustment of ceritinib should be reconsidered upon co-administration with itraconazole in ongoing clinical practice.

1H Nuclear Magnetic Resonance-based Metabolomics Study Reveals the Effects of Botrychium ternatum (Thunb.) Sw. on Bleomycin-induced Idiopathic Pulmonary Fibrosis in Rats

Mr. Yutao Lou[1], Dr. Xiaozhou Zou[1,2], Zhiyong Sun[1], Yiwen Zhang[1]
[1]Zhejiang Provincial People's Hospital, Hangzhou, China, [2]Key Laboratory of Endocrine Gland Diseases of Zhejiang Province, Hangzhou, China

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Botrychium ternatum (Thunb.) Sw. (BT) is a Chinese herbal medicine that has been shown to alleviate respiratory diseases, such as pulmonary hypertension and allergic asthma; however, its therapeutic effects and mechanisms in the treatment of idiopathic pulmonary fibrosis (IPF) are unclear.
Aim of the study: This study aims to assess the effects and potential mechanisms of BT on IPF.
Materials and methods: UPLC–TOF/MS and HPLC–UV analyses were used to explore the effective components and content in BT extract. An IPF rat model induced by bleomycin was used to evaluate the effects of BT. The pathological changes of lung tissue and the changes of biomarkers associated with fibrosis were detected. The metabolic regulatory mechanisms of BT on IPF were investigated using 1H-nuclear magnetic resonance-based metabolomics combined with multivariate statistical analysis.
Results: BT administration did not significantly reduce the body weights of IPF model rats, whereas pirfenidone did. Biochemical analysis revealed that BT notably suppressed the expression of hydroxyproline and transforming growth factor-β1 in the pulmonary tissue. Hematoxylin and eosin and Masson's trichrome staining showed that BT substantially improved the structure of the damaged lung and significantly inhibited the proliferation of collagen fibers and the deposition of extracellular matrix. Serum metabolomic analysis suggested that BT may exert antifibrotic effects by synergistically regulating phenylalanine, tyrosine and tryptophan biosynthesis; butanoate metabolism; synthesis and degradation of ketone bodies; tyrosine metabolism; and histidine metabolism.
Conclusion: This study was the first to clarify the potential antifibrotic mechanism of BT and provided a theoretical basis for developing BT as an effective antifibrotic agent.

Pro-arrhythmic effect of escitalopram and citalopram at serum concentrations commonly observed in older patients – a study based on a cohort of 19 742 patients

PhD student Pari Faraj, PhD Elisabet Størset, Associate professor Kristine Hole, Professor Godfrey Smith, Professor Espen Molden, Erik Sveberg Dietrichs[1]
[1]Center For Psychopharmacology, , Norway

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Background: For a decade, patients have been advised against using high citalopram- and escitalopram-doses due to risk for ventricular arrhythmia and cardiac arrest. Still, these drugs are widely used to treat depression and anxiety especially in older patients. It is unclear why they are cardiotoxic and at what serum concentrations patients are at risk for arrhythmias. Thus, how many patients that are at risk for iatrogenic cardiac arrest is unknown.
Methods: We studied the arrhythmogenic effects of citalopram, escitalopram and their metabolites on human cardiomyocytes. Concentrations showing pro-arrhythmic activity were compared with observed drug and metabolite serum concentrations in a cohort of 19 742 patients (age 12-105 years) using escitalopram or citalopram. As arrhythmia-risk is related to maximum serum concentration, this was simulated for different age-groups from the escitalopram patient material.
Results: Therapeutic concentrations of both citalopram and escitalopram but not their metabolites showed pro-arrhythmic changes in the human cardiac action potential. Due to age-dependent reduction of drug clearance, the proportion of patients above threshold for arrhythmia-risk increased with age. 20% of patients >65 years were predicted to reach potentially pro-arrhythmic concentrations, following intake of 10 mg escitalopram.
Conclussion: All patients that are using escitalopram or citalopram and have genetic substrates for acquired long-QT syndrome, are >65 years, are using additional pro-arrhythmic drugs or have predisposition for arrhythmias, should be monitored with therapeutic drug monitoring (TDM) to avoid exposure to potentially cardiotoxic concentrations. Serum concentrations should be kept below 100 nM, to reduce arrhythmia-risk.

Toxicological safety assessment of pyridazine analogues: an antitubercular agent

Ravinesh Mishra[1], Dr Anees Siddiqui[2]
[1]School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences & Technology, Baddi, India, [2]Faculty of Pharmacy, Jamia Hamdard, Hamdard Nagar, India

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

The continuing spread of drug-resistant tuberculosis is one of the most urgent and difficult challenges facing global TB control. Patients who are infected with strains resistant to isoniazid and rifampicin, called multidrug-resistant (MDR) TB, are practically incurable by standard first-line treatment. That's why there is an urgency to develop new drugs and strategies to fight against tuberculosis or a tragedy may occur. A novel series of 5,6-dihydropyridazine-1(4H)-carbohydrazides and its analogs was synthesized and characterized spectroscopically. All the compounds were characterized and screened for in vitro anti-tuberculosis activity against Mycobacterium tuberculosis H37Rv strains by using resazurin assay utilizing microtiterplate method. These compounds also showed good antitubercular. Thus, the high level of activity shown by the carbohydrazides suggests that these compounds could serve as leads for development of novel synthetic compounds with enhanced anti-TB activity. A toxicological safety assessment was conducted on 5,6-dihydropyridazine-1(4H)-carbohydrazides, to predict safety with oral consumption by rats. Two genotoxicity studies were conducted and no evidence of mutagenicity or genotoxicity was observed in the presence or absence of a rat liver S9 metabolic activation system at concentrations up to 5000 µg of compound/plate in a chromosomal aberration assay. Studies conducted in Wistar rats included a 14-day acute oral toxicity study, and a 90-day repeated oral toxicity study. A 6-month repeated oral toxicity study was conducted in rats. In the 14-day study, the NOAEL was determined to be 5 g/kg bw. While a few statistically significant ($p<0.05$) findings were observed in the 90-day Wistar rat study, it was considered to be a sound basis for conducting a 6-month study. In the 6-month study, the no observed effect level was concluded as 1,000 mg/kg bw/d, the highest dose group tested. Finally, in a developmental toxicity study in rats no fetal abnormalities related to administration of the test article were observed.

Simultaneous Determination of Exogenous Melatonin and of its Metabolite 6-Hydroxymelatonin in Saliva by Online Solid-phase Extraction Coupled with Liquid Chromatography-tandem Mass Spectrometry in Patients with Epilepsy During Sleep Induction in Nap Electroencephalography

Michela Palmisani[1,2], Costanza Varesio[2,3], Valentina De Giorgis[2], Francesca Crema[1], Roberto Marchiselli[1], Francesca Scandale[1], Cinzia Fattore[2], Paola Rota[4,5], Guido Fedele[6], Valentina Franco[1,2]
[1]Clinical and Experimental Pharmacology Unit, Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, , Italy, [2]IRCCS Mondino Foundation, Pavia, Italy. Member of ERN-Epicare, , Italy, [3]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, , , [4]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy, , , [5]Institute for Molecular and Translational Cardiology (IMTC), San Donato Milanese, Milan, Italy, , , [6]Associazione Farmaceutici dell'Industria (AFI), Milan, , Italy

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction

Melatonin is a key hormone regulating circadian rhythms and the sleep–wake cycle and it has been demonstrated to be effective to treat sleep disturbances. In a recent survey aiming at assessing the strategies adopted in everyday clinical practice for sleep induction in different paediatric and adult epilepsy centres in Italy, melatonin was reported as the most commonly drug used for sleep induction [1]. However there is no consensus on the timing and melatonin doses to be used for electroencephalography (EEG) recordings. In this context we have developed a new simple, rapid, and sensitive method to monitor simultaneously exogenous melatonin and its metabolite 6-hydroxymelatonin in saliva by automated online solid-phase extraction coupled with liquid chromatography-tandem mass spectrometry (LC-MS).

Materials and Methods

After on-line solid phase extraction melatonin, 6-hydroxy-melatonin and the internal standard melatonin-d4 were separated on a C18 column under gradient conditions. This method was applied to the analysis of saliva samples of patients with epilepsy treated with an oral solution of melatonin at the dose of 3 or 5 mg depending on body weight (3 mg for patients < 15 kg; 5 mg for patients > 15 kg). In this randomized crossover study melatonin was administered as a single dose 30 minutes before the EEG recording and was compared with a group of patients receiving sleep deprivation represented by sleep deprivation of 50% of physiological sleep the night before EEG registration. Unstimulated oral fluid samples were taken 30 min after the EEG [2].

Results

The calibration curves for both analytes were linear (r =0.999) in the range of 25–3000 ng/mL for melatonin and 12.5-1500 ng/mL for 6-hydroxymelatonin. The limit of quantitation was 9 ng/mL for melatonin and 6 ng/mL for 6-hydroxymelatonin. The intra-day and inter-day precisions (relative standard deviations) were below 7% for melatonin and below 11% for 6-hydroxymelatonin. The intra-day and inter-day accuracy were within 92-112% for melatonin and 89-112% for 6-hydroxymelatonin. Mean melatonin and 6-hydroxymelatonin concentrations were 197 and 19 ng/mL respectively (n=27).

Discussions and Conclusions

The present method was fully validated according to the guidelines of the European Medicines Agency and successfully applied to monitor salivary levels of melatonin and 6-hydroxymelatonin in a randomized study aiming at assessing the efficacy of melatonin against sleep deprivation in inducing sleep for EEG recordings in children and young adult patients with epilepsy.

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Adherence monitoring of oral endocrine breast cancer therapies by LC-HRMS - Evaluation of four sample matrices

Cathy Michelle Jacobs[1], Prof. Dr. med. Julia C. Radosa[2], Dr. Lea Wagmann[1], Dr. med. Julia S. M. Zimmermann[2], Dr. med. Askin C. Kaya[2], Merle Doerk[2], Aylin Aygün[2], Prof. Dr. Markus R. Meyer[1], Dr Lea Wagmann[1]
[1]Department of Experimental and Clinical Toxicology, Saarland University, Homburg, Germany,
[2]Department of Gynaecology, Obstetrics and Reproductive Medicine, Saarland University Hospital, Homburg, Germany

Alternative Sampling Strategies 1, Møterom 1, september 25, 2023, 13:00 - 14:30

Introduction: Oral endocrine breast cancer therapies need to be taken over a long treatment period and are associated with considerable side-effects. Both factors can have an important impact on patient's adherence. This study aimed to evaluate the suitability of plasma and urine, as well as the alternative matrices finger prick blood (FPB) sampled by volumetric absorptive microsampling (VAMS) and oral fluid (OF) for adherence monitoring of oral endocrine breast cancer therapies. For this purpose, a validated analytical approach based on liquid chromatography (LC) coupled to high-resolution mass spectrometry (HRMS) covering the analytes abemaciclib, anastrozole, exemestane, letrozole, palbociclib, ribociclib, tamoxifen, and endoxifen, was used.

Materials and Methods: Sample preparation consisted of dilution using acetonitrile, centrifugation (OF), and evaporation (plasma, urine). VAMS were extracted using acetonitrile, followed by an evaporation. Processed samples were analyzed using reversed-phase ultra-high performance LC (ThermoFisher Accucore Phenyl-Hexyl column) and orbitrap HRMS. The MS was operated in full scan mode and quantification was based on isotope dilution. Matching samples (plasma, urine, FPB, OF) from over 50 patients were collected, analyzed, and compared.

Results: Chromatographic separation of analytes was achieved in less than 10 minutes and limits of quantification ranged from 1 to 1000 ng/mL depending on the analyte and matrix. Limits of quantification were higher for some analytes in alternative matrices. The analytical procedures were successfully validated in all matrices for most analytes meeting requirements for therapeutic drug monitoring. Quantification of analytes using isotope dilution required a matrix dependent correction factor for some analytes e.g., a factor of 1.6 for abemaciclib in plasma and urine. The analysis of patient samples showed that adherence assessment of oral breast cancer medication is possible using all four matrices with exception e.g., of letrozole in OF.

Discussions and Conclusions: Adherence monitoring of oral endocrine breast cancer therapies in four different sample matrices was possible using fast sample preparations and quantification based on isotope dilution. Therapeutic reference ranges for these medications were only available for plasma and the method covered those ranges except for exemestane. However, there is a need to establish reference ranges in VAMS and OF, since quantified results in matching samples varied amongst the different sample matrices. VAMS sampling was difficult in breast cancer patients due to often observed circulatory pathologies in fingers and for OF sampling, dry mouth syndrome was rarely observed. In most authentic urine samples, the parent compound could be detected. However, metabolite mining should be considered in urine and OF for the adherence assessment. At this point in time, plasma is the preferred sample matrix to assess the adherence to oral endocrine breast cancer therapies due to available reference ranges.

Adaptative strategy of tacrolimus dosage adjustments when combined with nirmatrelvir/ritonavir in kidney transplant recipients

Dr Lidvine Boland[2], Pr Arnaud Devresse[2], Dr Sébastien Briol[2], Dr Caroline Monchaud[3], Dr Stéphanie Belaiche[4], Pr Yannick Le Meur[5], Pr Vincent Haufroid[2], Dr Florian Lemaitre[1]
[1]Rennes University Hospital, Rennes, France, [2]Cliniques Universitaires Saint-Luc, UCLouvain, Brussels, Belgium, [3]Limoges University Hospital, Limoges, France, [4]Lille University Hospital, Lille, France, [5]Brest University Hospital, Brest, France

Immunosuppression 1, Sal D, september 25, 2023, 13:00 - 14:30

Introduction:
Nirmatrelvir/rironavir is the actual first-line treatment to prevent severe coronavirus infectious disease 19 (COVID-19) but its combination with tacrolimus is at-risk of drug-drug-interaction (DDI) leading to accumulation and toxicity. In this study, we present the results of tacrolimus-nirmatrelvir/ritonavir combination in kidney transplant patients based on the French national recommendations for DDI management. We also present the results of simulations aiming at proposing a novel tacrolimus dosage adjustment algorithm when combined with nirmatrelvir/ritonavir.

Material and methods:
Data from 22 kidney transplant patients treated with tacrolimus and receiving nirmatrelvir/ritonavir for COVID-19 have been modeled with MWPharm++. Tacrolimus area under the curve before and after the antiviral treatment (AUC0-120h) were estimated and compared as were: tacrolimus half-life, nadir tacrolimus concentration (Cnadir) and the maximal trough concentration reached during the tacrolimus restart phase at the end of the antiviral treatment (CMaxAfter).
The best strategy to restart tacrolimus after nirmatrelvir/ritonavir discontinuation was explored using simulations. The two extreme scenarios for metabolism recovery observed in the patients of the study have been tested with different strategies of tacrolimus restart. Simulations were: a restart of tacrolimus at 100% of the initial dose from day-7; from day-8 or from day-9; a restart at 50% of the dose prescribed from day-8 and then 100% from day-9; at 50% from day-9 and then 100% from day-10 and finally, at 50% from day-8 with 50% at day-9 and then 100% from day-10. The best compromise was choose by an adjudication committee composed of a nephrologist, a clinical pharmacist and two pharmacologists.

Results
Before the antiviral treatment, patients had a median tacrolimus trough concentration of 5.2 ng/mL (IQR: 4.6-6.7ng/mL), and concentration measured just before of immunosuppressive treatment restart was 4.0ng/mL (IQR: 3.4-5.0ng/mL). Estimated AUC0-120h before the nirmatrelvir/ritonavir was 900ng.h/mL (IQR: 684-1213ng.h/mL) and slightly decreases to 752ng.h/mL (IQR: 622-895ng.h/mL) after treatment. The median decrease was 11% with 4 outliers patients with a decrease of 47%, 62%, 68% and 82% respectively. Median estimated half-life was 212h with some extreme values (range: 87-712h). The predicted Cnadir was close to the concentration measured before nirmatrelvir/ritonavir (4.7ng/mL). The median CMaxAfter was 11.2ng/mL (IQR: 8.7-19.2ng/ml) with 13 (59%), 8 (36%) and 5 (23%) patients having a CMaxAfter >10ng/mL, >15ng/mL and >20ng/mL, respectively. However, creatinine measured shows limited difference with the baseline creatinine (+2.1%, IQR: -3.4-+6.8%). No patient was hospitalized for severe covid-19 or acute renal failure.
The best compromise for tacrolimus restart was retrieved for a restart of tacrolimus at 50% of the dose prescribed from day-8 and then 100% from day-9 (CMaxAfter was 3.8ng/mL in case of rapid metabolism recovery and 13.8ng/mL in case of low metabolism recovery).

Conclusion:

Real-life data shows that part of patients receiving the tacrolimus-nirmatrelvir/ritonavir combination exhibits tacrolimus accumulation when the treatment is restarted and the simulations made from these data shows that a strategy with 50% of the dose initially prescribed from day-8 and then 100% from day-9 ensure drug safety. Therapeutic drug monitoring is an invaluable tool in such combination cases and allows a real-time adjustment of tacrolimus drug dosage.

Detection of kidney transplant patients at risk to lose their graft: neural networks and interpretability

Dr. Clément Benoist[1], Dr Anders Asberg[2], Dr Marc Labriffe[1], Pr. Pierre Marquet[1], Pr. Jean-Baptiste Woillard[1], Dr Jean-Baptiste Woillard[1]
[1]Inserm, Pharmacology & Toxicology, U1248, Limoges, France, [2]Department of Transplantation Medicine, Oslo Universitary Hospital, Oslo, Norway

Pharmacometrics, Møterom 5, september 25, 2023, 13:00 - 14:30

Introduction:
Post-transplant follow-up after kidney transplantation include regular assessments of renal function, e.g. as estimated glomerular filtration rate (eGFR). Recurrent neural network can be used for the prediction of longitudinal data and particularly the long short-term memory (LSTM) neural networks are suitable for these kind of data. Machine learning allows very accurate predictions, but it has been shown that the more accurate the predictions are, the less explainable they are. Some methods have been developed for explainability based on variable importance (SHAP, LIME). A novel, and more intuitive, method call SimplEx (for Simple Example) has recently been proposed where comparison with similar patients is performed. SimplEx can be adapted to different machine learning algorithms (https://arxiv.org/abs/2110.15355).
In this context, the objectives of this work were (i) to develop a LSTM to predict the individual GFR with a time horizon of 1 year ahead based on the current and previous features and (ii) to implement the Simplex algorithm to compare the prediction with similar patients.
Material and method: Long-term follow-up data on 3819 kidney transplantations from the transplant registry at the Oslo university hospital in Norway were used. We built a LSTM to dynamically predict the eGFR values at a 12-months horizon based on the two previous eGFR values. Data were split into a training set (50 % of the transplantations), test set (25 %), and validation set (25 %) to prevent overfitting. Optimization of hyperparameters based on root mean squared error (RMSE) was performed. We implemented the SimplEx algorithm on a corpus of 100 randomly selected patients in the training set. We investigated the interpretability about the eGFR prediction in the test set by providing relevant examples from the predefined corpus.
Results: Seven longitudinal and six non longitudinal covariates, in addition to the current and previous eGFR, were used in the LSTM. The final RMSE was 10.4 mL/min/1.73m2. To illustrate the SimplEx, a patient predicted eGFR of 21.6 mL/min/1.73m² at 2 years based on his eGFR values at 3 months and 1 year was associated by the algorithm with a weight of 79% to a patient with a true GFR and a LSTM predicted GFR of 28.3 and 29.3 mL/min/1.73m², respectively, and with a weight of 21% to a patient with a true GFR and a LSTM predicted GFR of 21.7 and 24.4 ml/min/1.73m², respectively.
Discussion: In this work, we implemented successfully the SimplEx algorithm on LSTM for explainability by comparison of the eGFR prediction to similar patients. This allows increasing the trust in the prediction and can be used as an uncertainty interval for the individual prediction.

Simplified pharmacokinetic interaction study utilizing capillary microsampling performed by patients themselves – patiromer effect on tacrolimus

Professor Anders Åsberg[1,2], Dr Rasmus Kirkeskov Carlsen[1], Dr Nils Tore Vethe[3], MSc(pharm) Shadi Alipour[1], Dr Karsten Midtvedt[1], Dr Geir Mjøen[1]
[1]Department of Transplantation Medicine, Oslo University Hospital – Rikshospitalet, Oslo, Norway, [2]Department of Pharmacy, University of Oslo, Oslo, Norway, [3]Department of Pharmacology, Oslo University Hospital – Rikshospitalet, Oslo, Norway

Alternative Sampling Strategies 1, Møterom 1, september 25, 2023, 13:00 - 14:30

Introduction

Pharmacokinetic (PK) interaction studies are resource demanding with rich sampling for measurement of drug levels over an entire dose interval, typically 10-12 samples over 12 hours. The introduction of capillary finger-prick samples for clinical therapeutic drug monitoring has opened new horizons also in the field of clinical trials. Allowing patients to take necessary rich samples themselves not only demand less work for the laboratory but also allows for more “real-life” samples to be obtained.

The aim of the present study was to perform a PK interaction study investigating the effect of patiromer (a potassium binder) on tacrolimus (Tac) PK in kidney transplant recipients in the early phase after transplantation.

Material and Methods

In this prospective, open, single-center, crossover study, the aim was to include a total of 12 kidney transplant recipients with hyperkalemia (4.6-6.0 mmol/L) in the early post-transplant phase. Maintenance immunosuppressive therapy had to include Tac. Patients signed informed consent before inclusion and the study was approved by the regional ethics committee and the Norwegian Medicines Agency.

Included patients started with one week patiromer treatment (Veltassa®, 8.4 g/day), followed by a 12-hour Tac PK investigation where patiromer was administered 3 hours after individualized morning dose of Tac (Prograf®). Patiromer was then withdrawn for one week and a new 12-hour Tac PK investigation was performed. During each PK investigation 12 finger-prick capillary blood samples were obtained with the Mitra® volumetric absorptive microsampling device. The first 3 samples were obtained by healthcare professionals, the next 3 by the patient under supervision and the remaining 6 un-supervised at a location determined by the patient (home/patient hotel). The Mitra® devices were delivered to the laboratory the day after sampling and analyzed with a validated assay (UPLC-MS/MS). EMEA bioequivalence criteria were used to assess the potential PK interaction on data obtained by non-compartmental analyses.

Results

The capillary finger-prick sampling was successful in 98% (283 of 288 Mitra® samples) of the cases and full Tac AUC(0-12) were possible to determine for all 12 patients (67% males, mean age 64 ±13 years). The bioequivalence criteria were overheld, showing a mean ±SD Tac AUC(0-12) of 138 ±43 µg*h/L without vs 128 ±27 µg*h/L with coadministration of patiromer. No difference in Tac C(max) values were detected without or with patiromer (25 ±9 vs. 22 ±5 µg/L, respectively).

Discussion and Conclusion

This novel PK interaction study design, where patients were allowed to obtain most of the scheduled samples by self-taken finger-prick samples, was a success regarding study design. No relevant interaction by patriomer on Tac PK was shown. Finger-prick sampling by the patient was especially valuable in a study like this where coordinating several patients to the same investigation day was

difficult. This save both time and money for the investigator and also make it easier on the patient as they do not need to stay in the hospital for 13-14 hours during the PK days.

Intraindividual variability in absolute bioavailability and clearance of midazolam in healthy individuals

Dr Kine E Kvitne[1], MSc Ole Martin Drevland[1], MSc Nora Haugli[1], MSc Eline Skadberg[1], Dr Hasse Khiabani Zaré[2], Dr Anders Åsberg[1,3], Dr Ida Robertsen[1]
[1]Department of Pharmacy, University of Oslo, Oslo, Norway, [2]Department of Pharmacology, Oslo University Hospital, Oslo, Norway, [3]Department of Transplant Medicine, Oslo University Hospital, Oslo, Norway

Miscellaneous 1, Møterom 2, september 26, 2023, 13:00 - 14:30

Introduction: Midazolam is the preferred clinical probe drug for assessing CYP3A activity. We have previously shown substantial intraindividual variability in midazolam absolute bioavailability and clearance in patients with obesity before and after weight loss induced by gastric bypass or a strict diet. The objective was to describe intraindividual variability in absolute bioavailability and clearance of midazolam in healthy individuals without obesity.

Materials and Methods: This study included 33 healthy volunteers (28 ± 8 years, 21% males, BMI 23 ± 2.5 kg/m2) subjected to four pharmacokinetic investigations over a 2-month period (weeks 0, 2, 4, and 8). Semi-simultaneous oral (0-hour) and intravenous (2-hours later) midazolam dosing were used to assess absolute bioavailability and clearance of midazolam.

Results: At baseline, mean absolute bioavailability and clearance were 46 ± 18% and 31 ± 10 L/h, respectively. The mean coefficient of variation (CV) % for absolute bioavailability and clearance of midazolam were 26 ± 15% and 20 ± 10%, respectively. Approximately one third had a CV >30% for absolute bioavailability, while 13% had a CV >30% for clearance.

Discussions and Conclusions: On average, intraindividual variability in absolute bioavailability and clearance of midazolam was low to moderate, however, especially absolute bioavailability showed considerable variability in a relatively large proportion of the individuals.

A fast and simple test for amatoxins in human urine – Comparison of a lateral flow immunoassay with LC-HRMS/MS analysis

Aline Christin Vollmer[1], Thomas P Bambauer[1,2], Candace S Bever[3], Dr Lea Wagmann[1], Prof. Dr. Markus R Meyer[1]
[1]Departement of Experimental and Clinical Toxicology, Saarland University, Homburg, Germany, [2]Departement of Forensic Toxicology, Goethe University, Frankfurt, Germany, [3]Foodborne Toxin Detection and Prevention Research Unit, Department of Agriculture, Agricultural Research Service, Western Regional Research Center, Albany, United States of America

Clinical toxicology and drugs of misuse 1, Sal C, september 25, 2023, 13:00 - 14:30

Introduction: The consumption of amatoxin-containing mushrooms causes a high number of (fatal) intoxications each year all over the world. Fast and simple detection of amatoxins in human biosamples is desired in clinical toxicology. Therefore, the aim of this study was to compare the detection of amatoxins in human urine i) using a rapid lateral flow immunoassay (LFIA) and ii) using liquid chromatography coupled to high-resolution tandem mass spectrometry (LC-HRMS/MS).
Materials and Methods: In-house manufactured LFIA test strips were inserted into a commercially available immunoassay cartridge (P.I.A.2, Protzek Biotec) followed by the addition of 100 µL of human urine submitted to the laboratory for clinical toxicological analysis. After incubation for 10 min, data evaluation was performed visually and by using a Photo Scanner (Somikon) plus subsequent photo processing by Fiji ImageJ. For analytical confirmation, human urine samples were prepared for LC-HRMS/MS analysis using a solid-phase extraction-based sample preparation. For the comparative study, 48 human urines after suspected amatoxin intoxications were analyzed by LFIA and LC-HRMS/MS.
Results: Based on experimentally determined pixel intensity ratios, LFIA results were confirmed positive (0.0-0.21) or negative (>0.66). Three urine samples were tested positive for amatoxins using the LFIA. Subsequent LC-HRMS/MS analysis confirmed these results (limit of detection 5 ng/mL for alpha- and beta-amanitin). In 41 cases, the pixel intensity ratio was above 0.66 indicating no amatoxins in urine, which was in line with the LC-HRMS/MS analysis. Three urine samples analyzed by the LFIA with ratios between 0.22 and 0.66 allowed no unambiguous positive or negative assessment. In these cases, LC-HRMS/MS analysis revealed one positive and two negative results. In one case, the LFIA reported a negative result, after LC-HRMS/MS only alpha-amanitin was detectable.
Discussion and Conclusions: No elaborate sample preparation and little special equipment is needed for the detection of amatoxins using the LFIA. No false positive results were observed, but the comparative study only covers 48 human urines so far. However, LC-HRMS/MS analysis - or an alternative confirmation method - must be performed, particularly if the pixel intensity ratio does not indicate a clear positive or negative result.

Detection of dichlorobisphenol-A (DCBPA) in hair following a single dose to female volunteers. A proof-of-concept study to demonstrate the interest of hair as a biomarker of exposure to endocrine disrupting compounds.

Julien Robin[1,2,3], PhD student Noémie Plattard[1,2,4], Doctor Antoine Dupuis[1,2,3], Doctor Sami Haddad[4], Doctor Nicolas Venisse[1,2,3]
[1]EATHER Research Group, Inserm CIC 1402, University Hospital of Poitiers, Poitiers, France, [2]IHES Research Group, UMR CNRS 7267 EBI Laboratory, University of Poitiers, Poitiers, France, [3]Biology-Pharmacy-Public Health Department, University Hospital of Poitiers, Poitiers, France, [4]Department of Environmental and Occupational Health, School of Public Health, CReSP, Université de Montréal, Montreal, Canada

Toxicology -clinical and environmental, Sal C, september 26, 2023, 13:00 - 14:30

Chlorinated derivatives of bisphenol A (ClxBPA) are products resulting from the chlorination of bisphenol A, especially due to the chlorine-based potabilization mechanisms of tap water. Four ClxBPA have been identified including dichlorobisphenol A (DCBPA). Regarding their effects on human health, numerous studies suggest that ClxBPA are endocrine disrupting compounds (EDC) suspected to promote metabolic diseases. Blood and urine are the main matrices used in human biomonitoring (HBM) although they are not suitable to evaluate long-time exposure to EDC with short half-life. Hair is an interesting alternative due to an accumulation of compounds during hair growth allowing a large exposure window. The main objective of this study was to determine concentrations in hair of volunteers after oral or dermal administrations of a single deuterated DCBPA (DCBPA-d12) dose to demonstrate the interest of hair as a biomarker of exposure to EDC.

This was an ancillary study of the PRECEPT study (PPC, 2020-A02116-33, IDRCB number). Five out of 12 healthy female adult volunteers gave their written informed consent to participate in the ancillary study. A single 50 µg/kg dose of DCBPA-d12 was administered either through oral (n = 2) or dermal (n = 3) route. After months, hair strands were collected, cut from the posterior vertex of the head close to the scalp. A segmental determination of DCBPA-d12 in hair samples was performed using a validated LC-MS/MS method (Robin et al. 2022). The study was approved by the National Agency for the Safety of Medicines and Health Products and the Protection of Persons Committee.

Two hair strands of 11 cm, two of 10 cm and one of 8 cm were collected after 5 to 9 months. Hair strands of 11 cm and 8 cm were segmented into 1 cm lengths while the two strands of 10 cm into 2 cm lengths. DCBPA-d12 was quantified in 3 out of 5 volunteers: 2 received the dermal dose and 1 the oral dose. DCBPA-d12 was quantified in a single distal segment at 0.024 ng/g and 0.050 ng/g in volunteers having received oral and dermal doses, respectively. For the last volunteer having received a dermal dose, DCBPAd12 was quantified into two successive distal segments at respectively 0.046 ng/g and 0.111 ng/g.

This is the first study reporting DCBPA-d12 transfer in hair after oral and dermal administrations. The study was focused on DCBPA as it is the main ClxBPA detected in HBM studies. The deuterated form of DCBPA was used to overcome basal DCBPA contamination in human body. DCBPA-d12 was solely found in one or two hair segments per volunteer suggesting that even exposure to a single dose of an EDC can be identified in hair through segmental analysis. DCBPA-d12 was entirely quantified in the distal sections highlighting diffusion along the hair shaft of compounds, stable over time when trapped in the hair. This study confirms the interest of hair as a biomarker of exposure to EDC. In the future, our objective is to develop a toxicokinetic model to relate hair concentrations to the overall EDC body burden.

Log P and Log D are good descriptors for assessing the choice between standard, gel or mechanical separator tubes for therapeutic drug monitoring/toxicology screening procedures.

Mme Ekaterina Iakovleva[1], Dr Aurelien Schrapp[2], Dr Fabien Lamoureux[2,3], Dr Emmanuel Bourgogne[1,4]
[1]laboratoire de pharmacologie/toxicologie, hopital Bichat, AP-HP, Paris, France, [2]laboratoire de pharmacologie/toxicologie et pharmacogénétique, CHU Rouen, Rouen, France, [3]Inserm U1096, Université de Normandie, UNIROUEN, Rouen, France, [4]laboratoire de toxicologie, Pharmacie, Faculté de Santé, Université Paris Cité, Paris, France

Miscellaneous 1, Møterom 2, september 26, 2023, 13:00 - 14:30

Introduction :
Recovery data of drugs in gel-based or mechanical separation blood collection tubes are lacking for therapeutic drug monitoring or clinical toxicology. Different experiments already studied the impact of gel separator tubes on common therapeutic drugs and found a correlation between physico-chemical properties and recovery. The study explored the impact of BD Vacutainer® PST™ II and Barricor™ separators on the recovery of a panel of 167 common drugs. Our objectives were to set and compare a log P and log D threshold value associated to a decreased drug recovery for these tubes.

Methods :
Of the 167 compounds, 13 were analgesics, 26 antidepressants, 12 anti-infectious agents, 25 anxiolytics, 29 cardiovascular drugs, 26 drugs of abuse, 13 neuroleptics and 23 other drugs. A 20 ng/mL mix for each drug was prepared in whole blood. Spiked blood were poured in the following sets: LH, PST™ II or Barricor™. After centrifugation, plasma was crushed with methanol. Supernatant (50 µL) was directly injected onto a reversed phase UPLC-MS/MS system, operated in positive mode in multiple reaction monitoring mode. Six samples for each condition allowed robust evaluation of dispersion and standard tube were used as control. Log P and log D values were calculated using MarvinSchetch 22.19 software. Statistical analyses were performed using R v4.2.3 and graphprism v8 softwares.

Results :
As expected, the impact of PST™ II gel on drugs recovery was variable according to the drugs families. Obtained results suggest a possible role of the drug chemical properties and led us to study the correlation between analyte recovery and the hydrophilic-lipophilic balance (log P). While log P is a useful parameter, it fails to account variation in the lipophilicity of a drug with respect to the ionic states present at key physiological pH values. Log D is calculated similarly but also considers the ionized form of the drug in the water. We observed a significant correlation between recoveries and logP ($R^2=0.29$) or log D values ($R^2=0.22$). A logP > 2.5 was estimated as a cut-off value at a 0.51 youden indice to predict a potent lack of drug recovery with an 89.3% sensitivity and a 62.1% specificity (ROC curve AUC=0.801). Similarly, a Log D > 1.59 was estimated as a cut-off value with a 85.7% sensitivity and a 68.5 % specificity (ROC curve AUC=0.78) at a 0.54 youden indice. For the BarricorTM tubes, results will be reviewed and discussed as well.

Conclusion :
Separator blood collection tubes are associated with a decrease in many drug concentrations, due to their composition as well as the considered drug classes and their physico-chemical characteristics. We propose a simple mean to assess the behavior of a given compound towards the gel by using either its logP or log D. A value below 2.5 or 1.59 for Log P and log D respectively, may generally allow the quantitation of a compound in blood drawn on PST™ II tubes, with Log D providing improvement for the majority of weak based ionized drugs at the relevant physiological pH.

Different drug annotation strategies in molecular networking approach on a panel of 60 patients : CFM-ID vs MetGem tools

Mr Sacha Guilhaumou[1], Dr Romain Magny[2,3], Dr Emmanuel Bourgogne[1,4]
[1]Laboratoire de toxicologie, Faculté de Santé, Pharmacie, Université Paris Cité, Paris, France, [2]Laboratoire de Toxicologie, Fédération de Toxicologie, Hôpital Lariboisière, AP-HP, Paris, France, [3]CiTCoM, CNRS, Université Paris Cité, Paris, France, [4]Laboratoire de Pharmacologie, hôpital Bichat, AP-HP, Paris, France

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction :
In clinical analysis or toxicology, untargeted screening remains a challenge, given the high number of molecules to be detected. LC-HRMS, the reference method for screening, generates a large volume of spectral data. Once acquired, a major issue lies in the absence of an exhaustive MS/MS database. To build databases, we can (i) inject standards and create an experimental database, (ii) use open-access or proprietary existing databases or (iii) build in silico databases using appropriate tools. We already demonstrated that cfm-predict tool from Competitive Fragmentation Modeling for metabolite IDentification (CFM-ID) library can be used to build an in-silico MS library of all commercialized drugs in France. Once the Molecular Network (MN) created, using a panel of 60 hospitalized patient's plasma, our objectives were to compare results obtained directly using the cfm-id (recognition queries) function vs conventional approach using MetGem software.

Methods :
Experimental spectra (patients) were acquired onto an LC-Orbitrap QExactive LC-HRMS system. For MS, positive MS (m/z 50-1500) and data-dependent MS/MS scans were recorded using CID and HCD activation types. In parallel, smiles structures of each drug were submitted to cfm-predict (cfm-id2.0) for generating in silico MS/MS spectra and compiling a database. Data preprocessing using MZmine was done prior to MN generation. The MN data was analyzed and visualized using either Metgem or directly subject to CFM-ID queries module for drug annotation. Thresholds for drug identification were set as 0.1 cosine + 3 fragments in MetGem, and as a 0.09 DotProduct score homology for cfm-id.

Results :
Using either cfm-id match function or MetGem, comparable results occurred. Compared to a reference method, we were able to confirm the presence of numerous drugs like acetololol, acebutolol, quetiapine, zolpidem, tramadol, amitryptiline.
The main difference between both strategies is the algorithm used to match candidates to spectra. Cfm-id strategy seems to offer slightly better results, but we were only able to compare those with reference methods, because samples were anonymized without access to their medical data.

Conclusion :
For screening, our results show that MN opens perspectives in clinical analysis or toxicology using LC-HRMS. Available databases being currently drug identification major bottleneck, CFM-ID library may be used with success to extend drug annotation. To this end, we are currently developing a web application to ease queriying, using patient .mgf file and in silico database as input to obtain putative annotations from our in silico database as output. On the other hand, cfm-predict module can also be used to generate MS/MS spectra, usable as an in-silico standalone database. It can then be queried via Metgem or Cytoscape, or even cfm-id matching function. Areas for improvement are still needed and consists, for example, in refining the generation of in-silico drugs MS/MS spectra and implementing thresholds to increase the ratio specificity vs. sensitivity.

CFM-ID : a tool for building drug databases AND increasing the drug annotation in clinical toxicology using High Resolution Mass Spectrometry and Molecular Network

M Sacha Guilhaumou[1], Dr Romain Magny[2,3], Dr Emmanuel Bourgogne[1,4]
[1]Laboratoire de Toxicologie, Faculté de Santé, Pharmacie, Université Paris Cité, Paris, France, [2]Laboratoire de Toxicologie, Fédération de Toxicologie, Hôpital Lariboisière, AP-HP , Paris, France, [3]CiTCoM, CNRS, Université Paris Cité, Paris, France, [4]Laboratoire de Pharmacologie, hôpital Bichat, AP-HP, Paris, France

Clinical toxicology and drugs of misuse 1, Sal C, september 25, 2023, 13:00 - 14:30

Introduction :
In clinical toxicology, analysts are confronted with problems, resulting in important clinical consequences. Untargeted LC-HRMS screening remains a challenge, given the high number of molecules to be detected. Once acquired, a major issue lies in the absence of an exhaustive MS/MS database. We already demonstrated Molecular network (MN) was an adequate strategy for screening. For creating database, CFM-ID was also an interesting tool able to build an in-silico MS/MS library of all commercialized drugs in France. Using a panel of 60 hospitalized patient's plasma, it was applied with relative success for drug's identification. Our objectives were (i) to improve this workflow and increase the rate of success using CFM-ID for drug queries also, (ii) to confirm our strategy on real patients, and (iii) to develop a web based application to annotate drugs found in patients plasma.

Methods :
An experimental database containing 122 drugs and a few metabolites was used as a starting point. Experimental spectra were acquired onto an LC-Orbitrap QExactive LC-HRMS system. For MS, positive MS (m/z 50-1500) and data-dependent MS/MS scans were recorded using CID activation types. For MN, data were analyzed and visualized using either CFM-ID or Metgem applications. In parallel, smiles structures of each drug were submitted to cfm-predict (CFM-ID v2.0) for generating in silico MS/MS spectra.

Results :
In a first step, using the in-silico cfm-predict module for MS/MS spectra generation and cfm-id for queries, a match was obtained for 83% of the molecules, even without a priori knowledge of the experimental MS/MS spectra. This ratio is higher compared to previous results obtained with MetGem. Both methods showed consistent results. This could be explained by the fact that there are no homology thresholds. Another limitation is that, without any thresholds, an answer will be given even if the homology is not clear. Scores (Jaccard or DotProduct) need to be assessed in order to increase specificity, and give pertinent results without reducing the sensitivity. In a second step, using a 0.1 threshold for DotProduct score, we applied this CFM-ID workflow to different patients. Drugs annotations were possible, enlarging the number of annotated compounds, even without standards available. Compared to a reference method, we were able to confirm the presence of numerous drugs like acetololol, quetiapine, zolpidem, tramadol, amitryptiline. Finally, a web application has been built.

Conclusion :
For screening, our results show that MN opens perspectives in clinical toxicology using LC-HRMS. Available databases are currently drug identification major bottleneck. CFM-ID may help to extend drug annotation, even without reference standards. To this end, we are currently developing a web application to ease querying using .mgf files as input and putative as output, in order to help clinicians to study poisonings. Areas for improvement are still needed and may consist in refining the

generation of in-silico drugs MS/MS spectra and implementing thresholds to increase the matching specificity.

Valproic acid intoxication: A case report of a pediatric case

Dr Maleke Sassi[1,2], Dr Sana Boujaafar[1,2,3], Dr Dorra Amor[1,2,3], Dr Dalèl Nasralli[4], Dr Fadwa Majdoub[4], Dr Refka Hassine[1,2,3], Dr Asma Benabdelaziz[1,2,3], Pr Nabila Ben Rejeb[1,2,3], Pr Asma Omezzine[1,2,3], Pr Jalel Chemli[4], Pr Ali Bouselama[1,2,3]

[1]Departement of biochemistry Hospital University Sahloul, Sousse, Tunisia, [2]Faculty of Pharmacy of Monastir , Monastir , tunisia , [3]University of Monastir , Monastir , Tunisia , [4]Departement of pediatrics Hospital university Sahloul, Sousse , Tunisia

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction:
Valproic acid (VPA) is a first-generation antiepileptic drug that is commonly used in the treatment of epilepsy and psychiatric diseases. Though rare, VPA intoxication is a clearly recognizable clinical scenario. It has a unique clinical characteristic when encountered, which can be easily handled. The main objective of this case report is to highlight and raise awareness among healthcare professionals about the management of VPA intoxication.
Material and methods: We describe a case of valproic acid intoxication who was admitted at the pediatrics department at the university hospital Sahloul in April 2023.
Results and discussion:
A 2-year-old male child with no medical history, was admitted at the emergency department after an accidental intake of sixteen tablets of VPA each containing 500 mg which correspond to 8000 mg of VPA (571mg/kg in this case). The patient was admitted four hours after swallowing the drug. He was drowsy with a Glasgow coma scale of 3/15. Therefore, the gastric lavage was not performed. He presented a quiet coma, a tachycardia and a typical bilateral miosis so controlled artificial ventilation was required. The therapeutic drug monitoring of VPA confirmed a high level of blood concentration (459.52 mg/L). (Toxicity threshold: 200mg/L). The patient presented a metabolic acidosis (pH = 7.23, NR : 7.35 – 7.45), an hyperosmolality (303.5 mosm/L, NR : 290 +/- 5mosm/L) and a moderate hepato-cytolysis was noted (ASAT :64 UI/L, NR : 10-50UI/L). The patient was transferred to the ICU where he received an intravenous loading dose of L-carnitine (150mg/kg), followed by a maintaince dose of 25mg/kg each 6 hours. Significant clinical improvements have been noticed within almost 2 days with a normalization of all his laboratory results.
Conclusion:
Understanding the common VPA intoxication symptoms might help with an early diagnosis and a successful treatment. We reported a successful treatment with L-carnitine. Nevertheless, other removal strategies as hemodiafiltration might be necessary to manage patients with a more severe acute VPA intoxication.

Phosphatidylethanol as a biological marker for alcohol consumption: Results from 24 574 subjects included in the HUNT4 Study

Phd Ragnhild Bergene Skråstad[1,2], Trond Oskar Aamo[1], Trine Naalsund Andreassen[1], Hilde Havnen[1], Kristian Hveem[3,4], Steinar Krokstad[4], Øyvind Salvesen[5], Olav Spigset[1,2]
[1]Department Of Clinical Pharmacology, St. Olav University Hospital , Trondheim, Norge, [2]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norge, [3]K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, Faculty of Medicine and Health Science, Norwegian University of Science and Technology, Trondheim, Norge, [4]HUNT Research Centre, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Levanger, Norge, [5]Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norge

Clinical toxicology and drugs of misuse 1, Sal C, september 25, 2023, 13:00 - 14:30

Introduction: Phosphatidylethanol 16:0/18:1 (PEth) is a sensitive and specific marker of alcohol consumtion. The aim of the present study was to investigate the association between self-reported alcohol consumption and PEth concentrations in a large general population study, and discuss optimal cut-off PEth concentrations for defined levels of alcohol consumption.

Materials and methods: A population based, longitudinal cohort study including 24 574 adults from the Trøndelag Health Study 4 (HUNT4) conducted in Trøndelag County, Norway. All residents who were 20 years of age or older in the study period (between September 2017 and February 2019), living in Nord-Trøndelag, were invited to participate in the study. The study consisted of questionnaires, clinical examinations and collection of biological material. Data included PEth concentration (measured in venous blood samples), self-reported alcohol consumption and CAGE score. Receiver operating characteristic (ROC) curves were created to investigate the relationship between PEth concentration and self-reported alcohol consumption over certain levels, and to identify possible optimum cut-off points.

Results: Of the blood samples, 15 038 (61.2%) had a PEth concentration below the lower limit of quantification (<0.030 µmol/l), 8407 (34.2%) had a concentration between 0.030 and 0.300 µmol/l and 1129 (4.6 %) had a concentration above 0.300 µmol/l. PEth levels increased significantly with the frequency of binge drinking, the frequency of alcohol consumption, the number of alcohol units consumed and the CAGE score. Among those with a PEth concentration > 0.300 µmol/l, almost 40% had a CAGE score of 2 or higher.

ROC curve analyses revealed that the cut-off concentrations with highest combined sensitivity and specificity were 0.057 µmol/l (40 ng/ml) for identification of those consuming >1 alcohol unit per day (sensitivity 86%, specificity 76%), 0.087 µmol/l (61 ng/ml) for consuming >2 units per day (sensitivity 87%, specificity 81%) and 0.122 µmol/l (86 ng/ml) for consuming >3 alcohol units per day (sensitivity 80% specificity 86%). By defining a CAGE score ≥2 as potentially harmful consumption, a cut-off of 0.100 µmol/l (70 ng/ml) identified 52 % of all those subjects.

Discussions and conclusions: We suggest that the cut-off limits of PEth concentrations take into account the indication for sampling. In a clinical setting, where all potentially harmful alcohol consumption should be identified, a high sensitivity is usually preferred at the expense of a lower specificity. In this case we suggest a cut-off as low as 0.03-0.06 µmol/l (or 20-40 ng/ml) depending on whether >1 or >2 alcohol units per day are considered of interest to detect. However, ethanol is a legal intoxicant and the consumers may tolerate some risk associated with its use. With a slightly more liberal threshold of about three units per day, a cut-off of 0.1 µmol/l (or 70 ng/ml) is yielding a high sensitivity with acceptable specificity. By contrast, in legal contexts where specificity is crucial, a

higher cut-off should be chosen. One should also predefine what level of alcohol consumption that is regarded as inappropriate before choosing cut-off.

The study has been published in Alcohol and Alcoholism Mar 2023 16;agad015. doi: 10.1093/alcalc/agad015

Presence of a cocktail of endocrine disruptors in the breast adipose tissue of women with and without cancerous lesions.

PhD student Luyao Wu[1], Julien Robin[1,2,3], Doctor Marion Albouy[1,2,3], Doctor Cédric Nadeau[4], Doctor Virginie Migeot[5], Doctor Antoine Dupuis[1,2,3], Dcotor Guillaume Binson[1,2,3], Doctor Nicolas Venisse[1,2,3]
[1]IHES Research Group, UMR CNRS 7267 EBI Laboratory, University of Poitiers, Poitiers, France, [2]EATHER Research Group, Inserm CIC 1402, University Hospital of Poitiers, Poitiers, France, [3]Biology-Pharmacy-Public Health Department, University Hospital of Poitiers, Poitiers, France, [4]Obstetrics and Gynaecology Department, University Hospital of Poitiers, Poitiers, France, [5]Public Health Department, University Hospital of Rennes, Rennes, France

Toxicology -clinical and environmental, Sal C, september 26, 2023, 13:00 - 14:30

Bisphenols (BPs) and parabens (PBs) are known or suspected endocrine disruptors (EDs) (www.EDlists.org) that can alter the normal functioning of the endocrine system. They could be linked to numerous pathologies, including breast cancer. Due to their lipophilicity, the accumulation of these EDs in adipose tissue is possible. The objective of this study was to measure several bisphenol A substitutes (BPS, BPF, and BPAF) and parabens in breast adipose tissue of women with cancerous and non-cancerous breast lesions.

Breast adipose tissue samples (n = 31) were collected as part of the BREDI (Breast Endocrine Disruptors Investigation) study. It was a prospective monocentric cohort study approved by a Research Ethics Committee (CPP Sud-Ouest II, n°12.11.39). Women aged over 18 year-old hospitalized for breast surgery at the University Hospital of Poitiers could be enrolled. Women receiving breast surgery for benign breast lesions, breast epithelial atypia and confirmed breast cancer were included. All participants in the study gave their informed written consent and the study was conducted in accordance with the Declaration of Helsinki. The concentrations of BPS, BPF, BPAF, methyl-, ethyl-, propyl- and butylparaben were quantified by a validated liquid chromatography-tandem mass spectrometry assay.

The detection frequency of endocrine disruptors in breast fat tissue ranged from 13% for BPF to 90% for methylparaben. The frequencies of quantification were lower, ranging from 3% for BPS to 52% for methylparaben. Mean +/- SD concentrations of methylparaben were higher in patients with cancerous lesions (8.5 +/- 11.8 ng/g, n = 13) and patients with epithelial atypia (6.5 +/- 9.3 ng/g, n = 9) than in patients with benign lesions (0.6 +/- 1.1 ng/g, n = 9). This study identified a cocktail of endocrine disruptor in breast adipose tissue. The relationship between methylparaben exposure and breast cancer needs to be further investigated.

Delayed Neurological Sequelae after Accidental CO-intoxication or Post Traumatic Stress from a Near-Death Experience?

MD, PhD Ingebjørg Gustavsen[1], MD, PhD Einar August Høgestøl, MD,PhD Fridtjof Heyerdahl
[1]Department of Pharmacology, Oslo University Hospital, , Norway

Toxicology -clinical and environmental, Sal C, september 26, 2023, 13:00 - 14:30

1. Introduction

A carbon monoxide (CO) intoxication may lead to death, or survival with or without long-term sequelae. The main causes of CO-intoxication is either accidental or with suicidal intent. A possible severe CO-intoxication consequence is Delayed Neurological Sequelae (DNS). Common DNS symptoms are declined cognitive capacity, fatigue, reduced psychomotor tempo, impaired gait, Parkinsonism, and diverse psychiatric symptoms. The long-term prognosis of DNS is unclear. Another obvious cause of psychiatric symptoms following CO-intoxication may be the near-death experience itself.
This case present an accidental CO-intoxication to a family of five. We address their symptoms the following years, in relation to documented literature.

2. Materials and Methods

A family with two adults and three children aged 10, 15 and 16 years got exposed to CO during an outdoor recreation activity in 2016. Four of the five family members had acute signs of CO-intoxication (e.g. confusion, hallucinations, seizures and/or coma). The mother and one of the children were hospitalized overnight due to severe acute symptoms, and received 2L/min of normobaric oxygen. Retrospective calculations from measured HbCO%, indicate HbCO-values of > 50% in these two victims on site. The other family members were not hospitalized or examined.

3. Results

The mother experienced DNS symptoms from day two after the CO-intoxication, with severe cognitive and neurological declines. She received hospital treatment with high-dose corticosteroids 8 weeks after the DNS onset, followed by a gradually remission. She returned to full-time employment after half a year.
The father and the two acutely affected children had no certain time-point of DNS onset, but were gradually affected by a number of neurological and psychiatric symptoms during the following years. The psychiatric symptom-intensity reached a maximum between 3-5 years. The most severe symptoms lasted several months, and needed health care treatment and certain temporary considerations related to work, school, and family situation.
All members of the family seemed to reach back to their habitual status and level of high achievement around six years after the CO-intoxication.

4. Discussions and Conclusions

Out of a family of five, both adults and two of the children got incapacitating symptoms within five years after the CO-intoxication. Symptoms were partly consistent with classically described DNS, and partly consistent with other psychiatric symptoms such as post-traumatic stress disorder (PTSD). The psychiatric symptoms were complicated to interpret in relation to the CO-exposure, due to the symptom fluctuations and the long time-interval after the exposure. However, we found that both the psychiatric and neurological symptoms were identical to descriptions on other accidental CO-intoxication cases. Similar to our experiences, the psychiatric burden reached a maximum 3-5 years after CO-exposure, while the cognitive and neurologic symptoms seemed to appear earlier.
This case suggests a hope for a complete remission several years after CO-intoxication. Nevertheless, there is a need to more research on CO-intoxication in all aspects, in particular to distinguish between possible toxic sequelae and the stress following a near-death experience.

Therapeutic drug monitoring for levetiracetam in pediatric patients with epilepsy: pharmacokinetics and therapeutic concertation range

Mr Yoshiaki Yamamoto[1], Ms. Akiko Ohta[1], Dr Naotaka Usui[1], Dr Katsumi Imai[1], Dr Yoshiyuki Kagawa[2], Dr Yukitoshi Takahashi[1]

[1]National Epilepsy Center, NHO, Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan, [2]Graduate School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, Japan

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction: The aims of this study were to assess the factor influencing the pharmacokinetics of levetiracetam (LEV) and to identify the therapeutic concentration range for LEV.
Materials and Methods: We retrospectively investigated 2413 serum LEV concentration obtained from 1398 pediatric patients (age, 0-15 years). Samples were grouped by age (infants, < 1 year; preschool children, 1-5 years; primary school children, 6-11 years; and adolescents, 12-15 years), and the LEV concentration-to-dose (CD) ratio was calculated. We reviewed seizure types and frequency and epilepsy types and syndromes. To evaluate the therapeutic concentration range for LEV, we selected patients according to the following criteria: (1) the clinical response was partially or completely achieved (>50% seizure frequency reduction (lasting more than 3 months)) and (2) the patients had good tolerance and remained on LEV therapy for more than three years. The study was approved by ethics review board of the National Epilepsy Center (Shizuoka, Japan, approval number 2016-28).
Results: The mean CD ratio was highest in adolescents (analysis of variance, $p < 0.001$); 22.5% and 15.7% higher in adolescents than in preschool children and school children, respectively (Scheffé test, $p < 0.001$); and higher in infants than in preschool children. Preschool children had the lowest ratio and tended to show an increase in the ratio from age 2 to 5 years. Use of enzyme-inducing antiseizure medication (phenytoin, carbamazepine, or phenobarbital) reduced the CD ratio by 6.1% in infants, 12.2% in preschool children, 5.9% in primary school children, and 9.4% in adolescents. The mean CD ratio was 2.7%, 26.9%, and 39.3% higher in preschool children, primary school children, and adolescents with defined chronic kidney disease (CKD) than in the respective age group of patients without CKD. The therapeutic concentration range for a long-term LEV therapy was 11 to 32 µg/mL.
Conclusions: LEV pharmacokinetics are significantly different between infant and preschool children, so TDM of LEV is clinically useful in these patients. In pediatric patients at higher risk for CKD, glomerular filtration rate and LEV levels should be carefully monitored.

Assessment of pentaerythrityl tetranitrate-metabolites in pregnant woman and sheep and elucidation of their placental transfer – Application of a validated liquid chromatographic mass spectrometric approach

Dr. Daniela Wissenbach[1], Dr. Silke Große[2], Prof. Tanja Groten[2], PD Dr. Frank T. Peters[1]
[1]Jena University Hospital, Institute for Forensic Medicine, Am Klinikum 1, Friedrich Schiller University Jena, Germany, Jena, Germany, [2]Jena University Hospital, Placenta Lab, Department of Obstetrics, Am Klinikum 1, Friedrich Schiller University Jena, Germany, Jena, Germany

Clinical toxicology and drugs of misuse 1, Sal C, september 25, 2023, 13:00 - 14:30

Introduction: Pentaerythrityl tetranitrate (PETN) has been used for treating ischemic heart disease for many years. Due to its vasodilative and vasoprotective effects it is presumed to have a positive impact in pregnant women with impaired placental blood flow. Several studies are currently conducted at Jena University Hospital to show a benefit for the newborn after application of PETN. The drug is rapidly metabolized to the active metabolites pentaerythrityl trinitrate (PETriN), pentaerythrityl dinitrate (PEDN) and pentaerythrityl mononitrate (PEMN). The aim of the present study was to monitor PETN concentrations in pregnant women and to obtain additional information about the human and ovine placental drug transfer of PETN and its metabolites.
Materials and Methods: In a prospective, randomized, double-blind, placebo controlled, parallel grouped, multi-center trial pregnant woman presenting with impaired uterine perfusion at mid gestation were randomized to oral intake of 100 mg PETN or placebo. Plasma samples were taken during the regular monthly control visits. Umbilical cord plasma was collected at birth (only at the study center in Jena). For the animal model, pregnant sheep were fed with 100 mg PETN daily. Serum samples were taken 2 h, 4 h and 24 h on three consecutive days after feeding. Samples and diluted samples (1:4) were analyzed with a validated method. A liquid-liquid extraction with ethyl acetate/2-propanol/dichloromethane mixture (60:20:20, v/v) was performed after adding the internal standards (1,3-Dinitroglycerin 0.001 mg/mL and 2-Mononitroglycerin 0.001 mg/mL). Chromatographic separation was performed by gradient elution on a Nucleoshell RP 18 plus column and analytes were detected by a Q Exactive Focus MS operated in negative ionization fullscan mode.
Results: 269 samples from pregnant women were analyzed. PETN and its metabolites was never detected in the 130 samples from the placebo group (53 women). PEMN and PEDN could be detected in 89 samples from the 139 samples from the verum group (46 women). The mean detectable PEMN concentration was 129 ng/mL (range 0.4 to 380 ng/mL) and the PEDN concentration was 14 ng/mL (range 0.2 to 48 ng/mL). One mother gave birth under PETN treatment. For the corresponding maternal and umbilical blood plasma samples PEDN was detected at concentrations of 3.3 ng/mL and 2.3 ng/mL, and PEMN at concentrations of 57 ng/mL and 73 ng/mL, respectively. PETN or PETriN were not detected. 184 ovine samples were collected from 21 animals at nine timepoints. While PETN could never be detected, traces of PETriN were present in about 10% of the fetal and maternal samples. PEDN and PEMN were detected in 91% of the samples taken at 2 h and 4 h after application, and were not detected in baseline and 24 h samples.
Conclusion: The method is suitable for the quantitative determination of PEDN and PEMN as well as a qualitative detection of PETriN in maternal and fetal ovine serum as well as in human plasma and cord blood plasma. As a result, it could be demonstrated for the first time that PEMN and PEDN can be detected in fetal samples after maternal intake of PETN during pregnancy.

Early tacrolimus exposure is associated with BK-viremia in kidney transplant recipients

M.d. Soufian Meziyerh[1,2], Aline L. van Rijn[3], Danny van der Helm[2], Paul J.M. van der Boog[1,2], Teun van Gelder[4], Aloysius C.M. Kroes[3], Johan W. de Fijter[1,2], Dirk Jan A.R. Moes[4], Joris I. Rotmans[1,2], Mariet C.W. Feltkamp[3], Aiko P.J. de Vries[1,2]
[1]Deprt. of Medicine, Div. of Nephrology, Leiden University Medical Center, 2333 ZA, Leiden, The Netherlands., Leiden, Netherlands, [2]LUMC Transplant Center, Leiden, Netherlands, [3]Deprt. of Medical Microbiology, Leiden University Medical Center, 2333 ZA, Leiden, The Netherlands., Leiden, Netherlands, [4]Deprt. of Clinical Pharmacy and Toxicology, Leiden University Medical Center, 2333 ZA, Leiden, The Netherlands., ,

Immunosuppression 1, Sal D, september 25, 2023, 13:00 - 14:30

There is scant evidence to what extent maintenance immunosuppression is quantitatively associated with BK viremia. We investigated the association between tacrolimus (tac) whole blood exposure and mycophenolic acid (mpa) plasma exposure with consecutive BK viremia within the first year posttransplant.

For this retrospective cohort study, 713 kidney transplant recipients (KTRs) transplanted at our center between 2013-2018 and treated with Tac, mpa and prednisolone, were selected from the local database. Both trough levels (C0) and area-under-the-curve (AUC) measurements of tac and BK viral loads were determined according to local protocol. Exposure measurements were carried backwards to assess exposure on landmarks: month 1.5, 3 and 6. Patients with no measurement of tac or mpa exposure within the first year due to switches were excluded, leaving 508 patients for analysis. Incidence and time to BK viremia (with load > limit of detection (LOD) and load > log 4) in the first year posttransplant were outcomes of interest. Hazard ratios (HR) of exposure to tac and mpa were assessed and adjusted for confounders such as donor and recipient age and gender, number of human leukocyte antigen (HLA) mismatch, days on dialysis, induction therapy, and living or deceased donation.

In total, 83 out of 508 (16%) KTRs developed a BK viremia (>LOD) in their first year post-transplant. Tac exposure (both C0 and AUC) on day 45 was significantly associated with subsequent development of BK viremia (load > LOD & load >log 4) with respectively unadjusted and adjusted HRs of 1.08 (95% CI: 1.02-1.14) and 1.08 (95% CI: 1.01-1.15) for 1 µg/L increase in C0 and 20 mg*h/L increase in AUC0-12h. Exposure of tac on day 90 or 120 was not associated with incident BK viremia. No association between exposure to mpa and BK-viremia was identified. Moreover, HR for tac remained unchanged if adjusted for mpa exposure and other transplant characteristics.

In our population, tac exposure on month 1.5 seems associated with incident BK viremia in a concentration-dependent manner. This was not found for mpa. The explanation for this finding could be that tacrolimus is a more potent suppressor of Th-lymphocytes which play a vital role in boosting viral immunity and memory. To the best of our knowledge, this is the first time that exposure to immunosuppressive drugs has been quantitatively associated with BK viremia. Future research is warranted to investigate causative and predictive impact of tac exposure on BK-incidence, which may aid physicians balance between toxicity and efficacy within the first year of transplantation.

Impact of incomplete clinical information on antibiotic's therapeutic drug monitoring interpretation

Dr Maeva Palayer[1], Dr Laurent Massias[1], Dr Emmanuel Bourgogne[1]
[1]laboratoire de pharmacologie, hôpital Bichat, AP-HP, Paris, France, [2]laboratoire de toxicologie, Faculté de Santé-Pharmacie, Université Paris Cité, Paris, France

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction
In clinical analysis, non-conformities in biological test request forms are undoubtedly frequent. Today, biologists are aware that errors present in these information have a direct negative impact on patient results interpretation and can alter diagnosis and medical treatment. The objectives were to record the various non-conformities over a period of 1 year and to investigate their impact on the therapeutic drug monitoring (TDM) results of anti-infectious agents, taking antibiotics as the target family.

Methods
A quantitative descriptive study of pre-analytical non-conformities (NC) was recorded in the pharmacology/toxicology laboratory of the Bichat Hospital. It was carried out over a period of 12 months and concerned all samples from the various clinical departments and care units of our hospital, as well as external samples.

Results
In 2022, we recorded 16875 cases of pre-analytical non-conformities out of 56014 samples received in our laboratory. These are by order of importance; missing time of last administration (43%), followed in almost equal proportions, missing dosages (29%), and missing routes of administration (23%). On the margin, the date and/or time of sampling is sometimes omitted. Similar results were obtained specifically for antibiotics. For these drugs, missing one of these information is important and could lead to erroneous interpretation as their measurement of treatment effectiveness is based on PK-PD indices (Cmax/MIC, AUC/MIC ratio, %T>MIC). Without complete clinical information it becomes difficult to interpret and/or advise on dosage adjustments. If the route of administration is missing, the therapeutic targets are different for continuous/discontinuous administration. In case of discontinuous administration, the time of the last dose is important to ensure that the interpretation is based on the though concentration. Finally, without dose regimen, the adaptation and proposal of a new dosage becomes impossible.
Inter individual variability (iiv) is important, especially in ICU patients and conduct to frequent under- or over-exposure. Our previous results notably showed that apart from ceftazidime, which is often in the therapeutic range, three other major antibiotics (piperacillin, cefepime and cefotaxime) were not in the therapeutic range in 67, 78, 61%, respectively, and overdosages could lead to neurotoxic effects. Beta-lactams are frequently administered by continuous infusion, which lead to an easier interpretation of the results than with discontinuous administration, as the time of last administration is not mandatory. However, the others informations are still crucial, especially for patients with reduced renal function.
Using reference guidelines for antibiotic concentration target, we will discuss, through different examples, the different pharmacological antibiotic interpretation and advice given to the clinical ward for dose adjustments and regimen.

Conclusion
Therapeutic drug monitoring of antibiotics is particularly important in populations with high pharmacokinetic variabilities, leading to unpredictable plasma concentrations and clinical outcomes. Rapid and accurate analytical methods are essential for real-time TDM but the quality of the sample information is of equal importance for an appropriate pharmacological interpretation.

Mycophenolic Acid Exposure Determines Antibody Formation Following SARS-CoV-2 Vaccination in Kidney Transplant Recipients: A Nested Cohort Study

M.d. Soufian Meziyerh[1,2], Pim Bouwmans[3,4], Teun van Gelder[5], Danny van der Helm[2], Lianne Messchendorp[6], Paul van der Boog[1,2], Johan de Fijter[1,2], Dirk Jan Moes[4], Aiko de Vries[1,2]
[1]Department of Medicine, Division of Nephrology, Leiden University Medical Center, Leiden, The Netherlands., , Netherlands, [2]Leiden University Medical Center Transplant Center, Leiden University Medical Center, Leiden, The Netherlands., , , [3]Department of Internal Medicine, Division of Nephrology, Maastricht University Medical Center, Maastricht, The Netherlands., , , [4]Cardiovascular Research Institute Maastricht School for Cardiovascular Disease, University of Maastricht, Maastricht, The Netherlands., , , [5]Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands., , , [6]Department of Nephrology, University Medical Center Groningen, Groningen, The Netherlands., ,

Immunosuppression 2, Sal D, september 26, 2023, 13:00 - 14:30

Despite (repeated) boosting, kidney transplant recipients (KTR) may remain at increased risk of severe COVID-19 since a substantial amount of individuals remain seronegative or with low antibody titers. In particular, mycophenolic acid (MPA) use has been shown to affect antibody formation negatively and may be an important modifiable risk factor.

We investigated the exposure-response relationship between MPA area-under-the-curve0-12h (AUC0-12h) exposure and seroconversion including antibody titers after vaccination using mRNA-1273 SARS-CoV-2 vaccine (Moderna) in 316 KTR from our center that participated in the national Dutch RECOVAC LESS CoV-2 vaccination study.

After two vaccination doses, 162 (51%) KTR seroconverted. KTR treated with MPA showed less seroconversion and lower antibody titers compared to KTR without MPA (44% vs. 77%, and 36BAU/mL vs. 340BAU/mL; p<0.001). The mean MPA-AUC0-12h exposure was significantly lower in KTR who seroconverted compared to KTR who did not (39 vs. 29mg*h/L; p<0.001). High MPA exposure (± 90mg*h/L) and no exposure to MPA resulted in a seroconversion rate ranging from 10%-80%. Every 10mg*h/L increase in MPA-AUC0-12h gave an adjusted odds ratio for seroconversion of 0.87 (95% CI: 0.79-0.97; p=0.010) and 0.89 (95% CI: 0.85-0.93; p<0.001) for KTR on dual and triple maintenance immunosuppressive therapy, respectively. Higher MPA-AUC0-12h correlated with lower antibody titers (R-0.44,p<0.001)

This study demonstrates the exposure-response relationship between gold standard MPA exposure and antibody formation to support interventional studies investigating MPA adjustment to improve antibody formation after further boosting.

Population Pharmacokinetics, Pharmacogenomics, and Adverse Events of Osimertinib and its Two Active Metabolites, AZ5104 and AZ7550, in Japanese Patients with Advanced Non-small Cell Lung Cancer: A Prospective Observational Study

Dr. Emi Ishikawa[1], Senior Asst. Prof. Yuta Yokoyama[1,2], Ms. Chishima Haruna[2], Assoc. Prof. Kasai Hidefumi[3], Mr. Ouki Kuniyoshi[4], Mr. Kimura Motonori[5], Dr. Jun Hakamata[5], Mr. Hideo Nakada[5], Mr. Naoya Suehiro[5], Dr. Naoki Nakaya[6], Dr. Hideo Nakajima[6], Senior Asst. Prof. Shinnosuke Ikemura[7], Assoc. Prof. Hiroyuki Yasuda[8], Assoc. Prof. Ichiro Kawada[8,9], Senior Asst. Prof. Hideki Terai[8,10], Asst. Prof. Aya Jibiki[2], Assoc. Prof. Hitoshi Kawazoe[1,2], Professor Kenzo Soejima[7], Gen. Hiroshi Muramatsu[5], Professor Sayo Suzuki[1,2], Professor Tomonori Nakamura[1,2]

[1]Division of Pharmaceutical Care Sciences, Keio University Graduate School of Pharmaceutical Sciences, Minato-ku, Japan, [2]Division of Pharmaceutical Care Sciences, Center for Social Pharmacy and Pharmaceutical Care Sciences, Keio University Faculty of Pharmacy, Minato-ku, Japan, [3]Laboratory of Pharmacometrics and Systems Pharmacology, Keio Frontier Research and Education Collaboration Square (K-FRECS) at Tonomachi, Keio University, Kawasaki-shi, Japan, [4]Department of Pharmacy, Ageo Central General Hospital, Ageo-shi, Japan, [5]Department of Pharmacy, Keio University Hospital, Shinjuku-ku, Japan, [6]Department of Oncology, Ageo Central General Hospital, Ageo-shi, Japan, [7]Department of Respiratory Medicine, Graduate School of Medicine, University of Yamanashi, Chuo-shi, Japan, [8]Division of Pulmonary Medicine, Department of Medicine, Keio University School of Medicine, Shinjuku-ku, Japan, [9]Health Center, Keio University, Yokohama-shi, Japan, [10]Keio Cancer Center, School of Medicine, Keio University School of Medicine, Shinjuku-ku, Japan

Oncology, Møterom 2, september 25, 2023, 13:00 - 14:30

Introduction

Novel strategies for managing adverse events (AEs) associated with osimertinib therapy include therapeutic drug monitoring and the use of biomarkers; however, these strategies remain poorly explored. Herein, we aimed to identify the association between (1) exposure to the osimertinib parent compound and its active metabolites (AZ5104 and AZ7550) and AEs and (2) germline polymorphisms and AEs.

Materials and Methods

This prospective longitudinal observational study was conducted between February 2019 and April 2022. In total, 53 patients with advanced non-small cell lung cancer undergoing treatment with osimertinib (80 or 40 mg tablet/day) were enrolled, from whom 302 serum samples (51 before steady-state [SS] and 251 during SS) were opportunistically collected, followed by serum drug concentrations analysis. A population pharmacokinetic model was developed to estimate the area under the serum concentration-time curve from 0 to 24 h (AUC_{0-24}) for the parent compound, AZ5104, and AZ7550. The effects of covariates, including body weight and albumin levels at the time of serum collection, on clearance and volume of distribution were evaluated. Genotyping was performed by real-time PCR. AEs were scaled when serum samples were collected after reaching SS, and exposure-toxicity and pharmacogenomics-toxicity relationships were evaluated.

Results

Based on stepwise covariate analysis, significant covariates were albumin for the clearance of the parent compound and AZ5104, and body weight for AZ7550 clearance. AEs were evaluated in 51 patients. The AUC_{0-24} of AZ7550 was significantly high in patients experiencing grade ≥2 paronychia ($p = 0.043$) or anorexia ($p = 0.011$). The AUC_{0-24} of the parent compound and AZ5104 were high in patients experiencing grade ≥2 diarrhea ($p = 0.026$ and $p = 0.049$, respectively). Additionally, patients with the C/T genotype of EGFR rs2293348 and A/A genotype of rs4947492 had a higher frequency of severe AEs than patients with other genotypes (63% [n = 5] versus 19% [n = 8], $p = 0.019$; and 41% [n

= 9] versus 14% [n = 4], p = 0.050; respectively). Patients with G/A or A/A genotypes of ABCG2 rs2231137 and C/T or T/T genotypes of ABCB1 rs1128503 had a higher frequency of any grade ≥2 AEs than patients with other genotypes (100% [n = 19] versus 69% [n = 22], p = 0.008; and 86% [n = 37] versus 50% [n = 4], p = 0.038; respectively).

Discussions and Conclusions

To the best of our knowledge, this study is the first to identify that high exposure to active metabolites and germline polymorphisms in EGFR, ABCG2, and ABCB1 could be significantly associated with higher severity of AEs. The correlation between the blood concentration of the parent compound and the AE occurrence has been previously studied but remains controversial. Our results expand on the available literature, suggesting that active metabolites of osimertinib, with 15 times higher potency or a longer half-life than the parent compound, may be key compounds for osimertinib AE management.

In conclusion, monitoring exposure to AZ5104 and AZ7550 and germline polymorphisms in EGFR, ABCG2, and ABCB1 may be an effective strategy for osimertinib AE management.

Development and Validation of an HPLC-UV method for Determination of Ceftobiprole in human serum

PhD Valeria Marini[1,2], Medical Resident in Clinical Pharmacology and Toxicology Fabio Sacco[1,2], Medical Resident in Clinical Pharmacology and Toxicology Michela Caviglia[1,2], Fabio Piras[1,2], Medical Resident in Clinical Pharmacology and Toxicology Fabio Piras[1,2], Doctor of Medicine Silvia Boni[3], Director Emanuele Pontali[3], Professor Francesca Mattioli[1,2]
[1]Department of Internal Medicine- University of Genoa , Genoa, Italy, [2]Clinical Pharmacology Unit , Galliera Hospital, Genoa, Italy, [3]Department of Infectious Diseases, Galliera Hospital, Genoa, Italy

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

INTRODUCTION

Ceftobiprole is a novel β-lactam antibiotic, approved and authorised in some countries as the prodrug ceftobiprole medocaril, under the trade name of Zevtera© or Mabelio © for the treatment of pneumonia. Ceftobiprole is administered as a 500 mg intravenous infusion over 2h every 8 h with dose adjustment according to the renal function. As for the other cephalosporins, it exhibits high inter-individual blood concentration variability that could impact its efficacy and toxicity. The aim of this study was to develop a simple and fast method for quantification of ceftobiprole in human serum applicable in therapeutic drug monitoring (TDM).

MATERIALS and METHODS

We used a high performance liquid chromatographic method with UV detection for the quantitative determination of ceftobiprole in small aliquot of human serum (100 ul). After a simple and fast protein precipitation by 30% sulphosalicylic acid, ceftobiprole was separated on a ultra biphenilic column (4,6 X150 mm, 5 µm) using a mobile phase composed of methanol and 10 mM phosphate buffer (pH 2,6) mixed in a linear gradient mode. Wavelength of UV detection was set at 320 nm.

RESULTS

Analysis time was 15 min per run. No interference from endogenous substances is observed during the elution of ceftobiprole. The retention time is 10,8 min. The method was validated for different parameters like precision, linearity, accuracy, limit of detection (LOD), limit of quantification (LOQ) according to ICH Q2 guidelines.Calibration curves were linear over the range of 0,5- 100 mg/L with a correlation coefficient above 0.998± 0,001.

DISCUSS AND CONCLUSION

The described method was developed for the quantification of ceftobiprole in human serum. The method was found to be accurate, precise, linear and reliable. The simplicity of sample preparation, the less expansive reagents, the use of small amounts of blood were the advantages of this analysis. This HPLC-UV method could be used for drug therapeutic monitoring of ceftobiprole,in particular in critically ill patients, and to assist the clinicians to perform real time dose adjustments based on trustworthy drug values.

Quantification of tacrolimus in scalp hair of lung and kidney transplant recipients

Ms Tanja Zijp[1], Ms Lenneke Junier[1], dr. Job Van Boven[1], dr. Tji Gan[1], prof.dr. Stephan Bakker[1], prof.dr. Daan Touw[1]
[1]UMCG, Groningen, Netherlands

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction: Tacrolimus is an immunosuppressant used to prevent graft rejection in lung and kidney transplant recipients. Tacrolimus blood concentrations are frequently measured for therapeutic drug monitoring, but only provide information on circulating concentrations at a single moment. Hair analysis may be of interest to assess adherence and tacrolimus tissue exposure over longer periods.
Aim: To develop a method to quantify tacrolimus concentrations in hair and to demonstrate its feasibility for lung and kidney transplant recipients.
Material and methods: An LC-MS/MS method was developed and validated following FDA and EMA guidelines, including stability and reproducibility in tacrolimus-positive hair. Approximately 20 mg of hair was washed and extracted with tacrolimus [^{13}C,$^{2}H4$] IS in methanol, under pulverisation with stainless steel balls in a mixer mill. Thereafter, the extract was centrifuged and filtered. Subsequently, 20 µl was injected on the LC-MS/MS. As proof-of-concept, lung and kidney transplant recipients visiting the outpatient clinic were asked to donate a lock of hair for method development. Hair colour and last measured tacrolimus whole-blood concentration were registered. Hair was taken from the occiput, stored at room temperature protected from light, and segmented in sections of 1–3 cm.
Results and discussion: The method was successfully validated, being linear between 0.05–5.0 µg/L hair extract (2.5–250 pg/mg hair), with slope 0.675 (SD=0.004) and intercept 0.006 (SD=0.000) with R^2 0.9995. Overall accuracy ranged from -2.5–5.5%, and within-run and between-run precision ranged from 0.9–5.3% and 0.0–2.4%, respectively. Homogenised hair was stable for 2.5 years at room temperature (bias: -10.47%) and -80°C (bias: -0.56%), with coefficients of variation between quintuplets of <5%. Moreover, the method was used to measure 17 hair segments from 6 transplant recipients, with black (n=1) and grey (n=5) hair. Median [min–max] hair tacrolimus concentration in the most proximal segment was 13.6 [11.7–18.0] pg/mg. Hair concentrations generally declined in the segments further away from the scalp.
Conclusion: Tacrolimus concentrations can be successfully measured in hair. This method will be used to investigate further relationships with tacrolimus exposure and adherence in lung and kidney transplant recipients.

Population pharmacokinetic modeling of CSF to blood clearance

Markus Hovd[1], Espen Mariussen[2,3], Hilde Uggerud[2], Aslan Lashkarivand[4], Hege Christensen[1], Geir Ringstad[5], PK Eide[3]
[1]Section for Pharmacology and Pharmaceutical Biosciences, Department of Pharmacy, University of Oslo, , Norway, [2]Norwegian Institute for Air Research, , Norway, [3]Department of Air Quality and Noise, Norwegian Institute of Public Health, , Norway, [4]Department of Neurosurgery, Oslo University Hospital, , Norway, [5]Division of Radiology and Nuclear Medicine, Department of Radiology, Oslo University Hospital, , Norway

Miscellaneous 1, Møterom 2, september 26, 2023, 13:00 - 14:30

Introduction
Quantitative measurements of cerebrospinal fluid (CSF) to blood clearance have previously not been established for neurological diseases. Possibly, variability in cerebrospinal fluid clearance may affect the underlying disease process and may possibly be a source of under- or over-dosage of intrathecally administered drugs. The aim of this study was to characterize the CSF to blood clearance of intrathecally administered substances, using the MRI contrast agent Gadobutrol (Gd). Improved understanding of CSF clearance may pave the way for therapeutic drug monitoring of intrathecally administered drugs such as methotrexate, which is associated with acute neurotoxicity.

Materials and Methods
Patients referred to the Department of Neurosurgery, who were examined for tentative CSF disorders and in whom intrathecal contrast enhanced MRI was considered indicated for were included. Gd was administered by intrathecal injection of 0.1-0.5 of 1 mmol/mL solution, after which blood samples and were collected up to 48 hours following administration. A population pharmacokinetic model was developed to describe individual pharmacokinetics of intrathecally administered Gd, and to determine its CSF to blood clearance.

Results
Population pharmacokinetic modelling based on 1140 blood samples from 161 individuals revealed marked inter-individual variability in pharmacokinetic profiles, including differences in absorption half-life (time to 50% of tracer absorbed from CSF to blood), time to maximum concentration in blood and the maximum concentration in blood as well as the area under the plasma concentration time curve from zero to infinity. In addition, the different disease categories of cerebrospinal fluid diseases demonstrated different profiles.

Dicussions and Conclusions
The present observations of considerable variation in CSF to blood clearance between individuals in general and across neurological diseases suggests that CSF to blood clearance may become a useful diagnostic tool. We also suggest that it may become useful for assessing clearance capacity of endogenous brain metabolites from cerebrospinal fluid, as well as measuring individual CSF to blood clearance of intrathecal drugs.

Use of vancomycin population pharmacokinetic model in pediatric patients with cystic fibrosis: impact of data on the predictive performance

Aysenur Yaliniz[1,2], Mathieu Blouin[1,2], Marie-Élaine Métras[2,3], Camille Gaudreault[4,5], Marie Christine Boulanger[4,5], Karine Cloutier[4,5], Marie-Hélène Dubé[4,5], Isabelle Viel-Thériault[5], Julie Autmizguine[6,7,8], Amélie Marsot[1,2,8]

[1]Laboratoire STP2, Faculté de Pharmacie, Université de Montréal, Montréal, Canada, , , [2]Faculté de Pharmacie, Université de Montréal, Montréal, Canada, , , [3]Département de Pharmacie, Centre Hospitalier Universitaire Sainte Justine, Montréal, Canada, , , [4]Faculté de Pharmacie, Université Laval, Québec, Canada, , , [5]Département de Pharmacie, Centre Hospitalier Universitaire de Québec-Université Laval, Québec, Canada, , , [6]Département de Pharmacologie, Faculté de Médecine, Université de Montréal, Montréal, Canada, , , [7]Unité de Pharmacologie Clinique, Centre Hospitalier Universitaire Sainte Justine, Montréal, Canada, , , [8]Centre de recherche, Centre Hospitalier Universitaire Sainte Justine, Montréal, Canada, ,

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction: Cystic fibrosis (CF) is the most common life-threatening illness in children and young adults in Canada. According to the Canadian 2020th Annual Data Report, Staphylococcus aureus is currently the most prevalent pulmonary pathogen encountered in pediatric CF patients. Vancomycin, a glycopeptide antibiotic used against Gram-positive bacterial infections, especially against Methicillin-resistant Staphylococcus aureus, is the first-line treatment according to the Infectious Disease Society of America. Its narrow therapeutic index and high interindividual pharmacokinetic (PK) variability make optimization of its dosing crucial. In 2020, updated vancomycin TDM guidelines have been published. These recommendations suggest targeting a ratio of area under the curve over 24 hours to minimum inhibitory concentration (AUC0-24/MIC) between 400 and 600 mg•h/L, preferably through the Bayesian method by using population pharmacokinetic (popPK) models. This study aims to assess the predictive performance of popPK models of vancomycin in pediatric CF patients.

Methods: Patient data from two centers in Canada (Centre Hospitalier Universitaire Sainte Justine (CHUSJ), Montréal and Centre mère-enfant Soleil (CMES), Québec) were collected from April 2018 to May 2022. A literature review was conducted through the PubMed database to identify all published vancomycin popPK models for pediatric CF patients. External evaluation of the identified models was performed by calculating prediction errors (PE) between model-predicted and observed concentrations using NONMEM (Icon Development, v7.5). Then, bias was assessed by calculating the median PE and imprecision by calculating the median absolute PE. The models' predictive performance was considered valid if its bias was within ±20% and its imprecision was ≤30%. The parameters were re-estimated if the obtained values of bias or imprecision for a model were not within the established ranges. Data from each center were evaluated separately and combined. Statistical analyses and data visualization were performed using Excel (v16.54) and R (v4.1.2).

Results: During the study period, 53 vancomycin concentrations were collected from six pediatric CF patients (mean age and weight ± SD: 11.3 ± 4.9 years and 33.5 ± 13.1 kg) of both centers. The mean ± SD administered vancomycin dose was 16.2 ± 3.1 mg/kg. Trough and peak concentrations data were available for CMES versus only trough concentrations for CHUSJ. Only one popPK model of vancomycin for pediatric CF patients was identified through the literature review. The external evaluation resulted in the following population bias and imprecision values [60.5%, 61.7%], [11.7%, 12.0%], [28.1%, 33.7%] for CHUSJ, CMES and both combined, respectively. A re-estimation of parameters was necessary to obtain values within the established ranges for both centers combined and the CHUSJ alone.

Conclusion: Despite vancomycin being used as a treatment for over 60 years, only one popPK model was identified for pediatric CF patients. External evaluation of the model, performed with different data from two centers, led to distinct results showing the importance of this step before using a model in clinical practice.

Development of the My-5FU immunoassay on the IDS-ISYS automate for therapeutic drug monitoring of 5-Fluorouracile

Benedicte Franck[1], Marie-José Ferrand-Sorre[1], Jodi Courtney[2], Florian Lemaitre[1], Marie-Clémence Verdier[1], Dr Camille Tron[1]
[1]Pharmacology department, University of Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) – UMR_S 1085, Rennes, France, [2]Saladax Biomedical, Inc., Bethlehem,

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction:
The clinical interest of 5-flurorouracile (5FU) therapeutic drug monitoring (TDM) has been reported in many studies to prevent toxicity and to identify patient with underexposure. Moreover, 5FU TDM is complementary to research of dihydropyrimidine deshydrogénase deficiency to adjust dosage according to actual drug exposure after a decrease of the first dose in case of deficiency. The immunoassay My5FU™ was validated on several analyzers but no application was reported on the multidiscipline automate ISYS from immunodiagnostics system (United Kingdom). We aim to report the analytical validation of the assay on this new instrument and the application to the analysis of 5FU plasma exposure in a cohort of patient in whom routine TDM was performed with My-5FU™ on a historical reference analyzer (Cobas® c 111, Roche).

Material and Methods:
The My-5FU™ kit was composed of two ready to use reagents, six calibrators and three levels of quality controls (QC) (225, 450, 900 ng/mL). Seven µL of plasma samples were mixed with 95 µL of each reagent. Performances of the assay on the ISYS were assessed by within day (n=10 replicates/ QC level) and between days (3 days) precision and accuracy, inter-samples contaminations, matrix effect (n=7 plasma sources spiked at 200 ng/mL), proficiency testing accuracy (n=12) and agreement of patients samples concentrations compared to the reference instrument (c111). Patients dosing regimen was continuous infusion for 46h. Coefficient of variation and bias compared to expected concentrations values within ± 15% were considered acceptable.

Results:
Within day and between days precisions were 2.6%/3.2%, 1.9%/2.5%, 2.2%/2.5% for QC low, medium, high respectively. Overall bias were -6.1%, -4.4%, -3.7% for QC low, medium, high respectively. No influence of high concentration samples was observed on accuracy of low concentrations samples (no cross contamination). Coefficient of variation of 5FU concentrations measured in 7 different sources of human plasma was 14.8 % (bias ranged from -6.7 to -17.6%). Bias to the nominal value of proficiency testing samples ranged from -9.9% to 1.6 % (mean: -1.9%). A set of 119 samples from patients treated with 5FU for digestive cancers was analyzed. Mean concentration was 420.7 ng/mL (median: 369.7 ng/mL, IQR 246.2-530.5 ng/mL), coefficient of variation was 68 %. A good correlation was found compared to the reference analyzer: Deming regression slope was 1.019, intercept was -13.5, R was 0.99, and mean bias was -1.8 ng/mL. Overall, 4.2% of samples were measured with a negative bias > -15% compared to the reference.

Discussion/Conclusion:
The immunoassay My-5FU™ showed good analytical performances on the automate ISYS. Good agreement was observed compared to the reference analyzer. Nevertheless, a negative bias outside the specification was observed in a few patients' samples suggesting a matrix effect that should be further explored. In addition, half of concentrations measured in this cohort of routine TDM were lower than 400 ng/mL that highlights that many patients are underexposed to 5FU (For 46h infusion, therapeutic range is about 430-650 ng/mL) meaning that flexible assay suitable for many analyzers could be helpful to widespread 5FU TDM in clinical practice.

Frequency of the CYP2C19*2 and CYP2C19*17 polymorphism in an Argentinian pediatric cohort and its effect on voriconazole plasma concentration.

Dr. Santiago Zugbi[1], Dra Verónica Araoz[1], Pharm. Juliana Testard[1], Bs. Milagros Dinardi[1], Bs. Christian Olivetti[1], Pharm. Lucas Brstilo[1], Dra. Adriana Sassone[1], Med. Fernanda Conde[1], Med. María Victoria Ponce[1], Med. Analía Julia[1], Dra. Cristina Alonso[1], Dra. Natalia Riva[3], Dra. Paula Schaiquevich[1,2], Paula Schaiquevich

[1]Hospital De Pediatría Garrahan, Buenos Aires, Argentina, [2]National Scientific and Technical Council, Buenos Aires, Argentina , [3]School of Pharmacy and Nutrition, University of Navarra, Pamplona, Spain

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Voriconazole is among the first-line antifungal drugs to treat invasive fungal infections in children and known for its pronounced inter- and intraindividual pharmacokinetic variability. The sources of variability are attributed non-linear kinetics, the potential for drug-drug interactions in addition to patient-specific characteristics such as gender, age and body weight. Polymorphisms in CYP2C19 involved in voriconazole metabolism, may explain serum concentrations and eventually the therapeutic outcome. Our objective was to genotype clinically relevant CYP2C19 variants and characterize a pediatric population to complement voriconazole therapeutic monitoring.
Forty patients with a prophylactic or therapeutic indication for voriconazole were included. Peripheral blood samples were extracted using commercial kits to obtain DNA and genotyping was performed using RFLP-PCR. Two hundred voriconazole trough concentrations (C0), corresponding to clinical routine, were quantified using high performance liquid chromatography-FLR in serum samples. The allele frequencies of the variants were analyzed and the metabolizer phenotype of each patient was correlated with C0. Additional data were extracted from the electronic medical records. Demographic, clinical and pharmacological factors were analyzed. An exploratory data analysis was performed using the Graphpad Prism V.8.
The CYP2C19*1 (wild-type), CYP2C19*2 (rs4244285) and CYP2C19*17 (rs12248560) variants were genotyped. The allele frequencies in our population were 13% and 9% for *2 and *17 respectively; obtaining 65%, 20%, 12.5% and 2.5% of normal (*1/*1), intermediate (*1/*2, *2/*17), rapid (*1/*17) and poor (*2/*2) metabolizer phenotypes respectively. Median dose-normalized voriconazole C0 plasma concentrations for the different groups were 3.51, 10.7, 3.2 and 27.10 µg/mL/mg/kg/day for normal, intermediate, rapid and poor metabolizer respectively. Statistical analysis showed a significant difference between all groups except for normal and rapid metabolizers ($p<0.002$).
These results are the first to show the frequency of the clinically relevant variants in a Argentine cohort and their effect on the pharmacokinetics of voriconazole. Understanding the factors affecting voriconazole pharmacokinetics in children is a prerequisite towards individualized dosing schemes to eventually improve the treatment outcome in children suffering from IFIs. From these data, it would be advisable to consider the variant of the patient prior to calculating the dosage of voriconazole. Further studies are needed to elucidate the relationships of demographic, clinical, and pharmacological factors for this cohort.

Oxycodone, morphine, and fentanyl in patients with chronic pain: Proposal of dose-specific concentration ranges

MD, PhD Cecilie Hasselø Thaulow[1], MD, PhD Arne Helland[2,3], MD, PhD Ulf Erik Kongsgaard[4,5], MD, PhD Gudrun Høiseth[1,5,6]

[1]Department of Forensic Sciences, Division of Laboratory Medicine, Oslo University Hospital, Oslo, Norway, [2]Department of Clinical Pharmacology, St. Olav University Hospital, Trondheim, Norway, [3]Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway, [4]Department of Anesthesiology, Division of Emergencies and Critical Care, Oslo University Hospital,, Oslo, Norway, [5]Institute of Clinical Medicine, Medical Faculty, University of Oslo, Oslo, Norway, [6]Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway

Miscellaneous 2, Møterom 5, september 26, 2023, 13:00 - 14:30

Introduction:
Therapeutic drug monitoring (TDM) of opioids may be warranted in case of suspected non-adherence, abuse or diversion, or in cases of therapeutic failure or adverse effects. In addition, opioid concentrations are often measured in forensic cases, such as driving under the influence, overdose deaths, poisoning, or chemical submission cases. However, a lack of reference concentration ranges hampers the interpretation. We therefore suggest dose-specific concentration ranges in serum for oxycodone, morphine and fentanyl, based on concentration measurements from a large number of patients using opioids for chronic pain.

Materials and methods:
Patients on opioids for various indications undergoing TDM, as well as a smaller group of patients with cancer receiving inpatient or outpatient care, were included in the study. The measured concentrations were grouped according to daily opioid dose intervals, and the distribution of serum concentrations in each dose interval was evaluated. Additionally, the expected average serum concentrations at steady state were calculated for each dose interval based on published pharmacokinetic data, and a targeted literature search for previously reported dose-specific concentrations was performed.

Results:
Opioid serum concentrations in 1054 patient samples were included: 1004 in the TDM group and 50 in the cancer group. In total, 607 oxycodone, 246 morphine, and 248 fentanyl samples were evaluated. The vast majority of patients on morphine or oxycodone used oral depot formulations, whereas all included patients on fentanyl used the patch formulation. Median (10–90th percentile) concentration/dose (C/D) ratios for all samples, irrespective of time between last dose and sampling, were 1.6 nM/(mg/24 h) (0.43–4.9) for oral oxycodone, 0.72 nM/(mg/24 h) (0.16–2.6) for oral morphine and 0.10 nM/(µg/h) (0.032–0.32) for fentanyl patch, respectively. We propose dose-specific concentration ranges (not shown in the abstract) based mainly on the 10–90th percentiles of the concentrations measured in patient samples, with some adjustments where the calculated average concentrations and previously published concentrations deviated from the patient samples.

Discussion and conclusion:
The proposed dose-specific ranges may be useful for interpreting steady-state opioid serum concentrations in both clinical and forensic settings. The ranges are not correlated to drug effects, and concentration measurements should be interpreted in light of clinical information.

Development of an LC-MS/MS method for the simultaneous determination of four antiepileptic drugs in dried plasma spots – Comparison of plasma generated by membrane filtration and by centrifugation

Biomedical laboratory Science Julia Mahunu Ngudie[1], PhD Michael Tekle[1], PhD Camilla Linder[1], Phd Victoria Barclay[1]
[1]Medical Unit for Clinical Pharmacology, Karolinska University Hospital, Sweden, Huddinge, Sverige
Alternative sampling strategies 2, Møterom 1, september 26, 2023, 13:00 - 14:30

Introduction: Therapeutic drug monitoring of the antiepileptic drugs (AEDs) carbamazepine, lamotrigine, levetiracetam and valproic acid is important in the treatment of epilepsy e.g., for dose adjustments. The aim of this project was to develop an LC-MS/MS method for these four AEDs in dried plasma spots (DPS). The dried plasma was generated by membrane filtration using two different types of membranes. The concentration of the AEDs in membrane generated plasma was compared with the concentration in centrifuged plasma from the same venous blood samples. The overall aim of this project was to evaluate the possibility to quantify the four AEDs as dried plasma spots, using plasma generated by the membrane filtration of whole blood.

Material and Method: Plasma was generated from venous whole blood samples by centrifugation or membrane filtration. The membrane filtration was performed using capillary extraction prototypes, provided by Capitainer. 70 µL of whole blood was pipetted onto the membrane. Plasma was generated by the blood filtering through the membrane with capillary force to a collection channel. Approximately 15-20 µL of plasma was obtained for further LC-MS/MS analysis as wet plasma or as dried plasma spots.
The dried plasma spots were prepared by pipetting 10 µL of plasma, calibrators, or quality controls onto Ahlstrom 222 chromatography paper discs. The spots were dried (≥ 12 h) before extraction (30 min at 450 rpm) with methanol (containing the internal standards). Aliquots of the methanol extracts were evaporated and reconstituted in 10 % mobile phase A in methanol. The samples were simultaneously analysed using an Acquity UPLC I-Class system coupled to a Xevo TQ-S micro mass spectrometer (Waters).

Results: The DPS method was validated, and acceptance criteria were met, according to the guideline on bioanalytical method validation given by the European Medicines Agency (EMEA). In addition to this, matrix effect, recovery, and process efficiency, were determined.
Quantification of carbamazepine, lamotrigine, levetiracetam and valproic acid by LC-MS/MS in the membrane generated plasma samples (≥ 10 samples per analyte) showed an acceptable correlation to concentrations in plasma obtained by centrifugation, $R2 = 0.90$ for carbamazepine, 0.95 for lamotrigine, 0.99 for levetiracetam and 0.97 for valproic acid.

Discussion and Conclusion: An LC-MS/MS method for AEDs in DPS was developed and validated. The concentrations in the two matrices, i.e., plasma generated by membrane filtration or centrifugation, were not the same. However, preliminary results in membrane generated plasma show a good correlation to concentrations in plasma generated by centrifugation. The presented method and the preliminary results are the first step for future LC-MS/MS measurements of AEDs sampled by finger pricks, where a plasma membrane generates “plasma like matrices” to be dried on Ahlstrom paper discs.

This project was partly founded by the strategic innovation programmes Swelife and Medtech4Health, both part of a shared investment in strategic innovation areas by Vinnova, the Swedish Energy Agency and Formas.

Development of a method for the quantification of fluoroquinolones and antiviral drugs using volumetric absorptive microsampling.

Dr Bénédicte Franck[1], Mrs Marie-José Ferrand-Sorre[1], Dr Camille Tron[1], Dr Marie-Clémence Verdier[1], Dr Florian Lemaitre[1]
[1]University of Rennes, Centre Hospitalier Universitaire Rennes, École des Hautes Études en Santé Publique, IRSET (Institut de Recherche en Santé, Environnement et Travail), UMR S 1085, Rennes, France. , Rennes, France

Alternative Sampling Strategies 1, Møterom 1, september 25, 2023, 13:00 - 14:30

Introduction :The therapeutic drug monitoring (TDM) of anti-infective drugs is increasingly performed in clinical practice. However, this TDM can be challenging in many cases, including TDM based on area under the concentration-time curve, at-home patients, and children.
Microsampling and in particular Volumetric absorptive microsampling (VAMS) is an innovative alternative sampling strategy to venous sampling which presents many advantages for therapeutic drug monitoring (TDM) : non-invasive, small volume of blood collected from a finger prick (10 µL), usable at-home and shippable to the pharmacology lab.
The goal of this study was to develop and validate an ultrahigh performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) method for the quantification of 3 fluoroquinolones (ciprofloxacin, ofloxacin, moxifloxacin) and 2 antivirals drugs (ganciclovir, aciclovir) in blood using VAMS.

Material & methods : Bloods were sampled using VAMS tips (Neoteryx®, Trajan) and dried away from light at room temperature (RT) for 2h. Blood was extracted from the tips using 200µL of water solution (water + internal standards: lomefloxacin and ganciclovir-D5) and sonication. Protein precipitation was performed by adding 300 µL of a mixture of zinc sulphate, acetonitrile and water 0.05M, followed by steps of vortex and centrifugation. Two and 10µL were injected in the LC-MS/MS system for fluoroquinolones and antiviral drugs, respectively. Elution was performed on a C18 reversed column and a mobile phase composed of Formic acid in water, water and acetonitrile.
The method was validated according to the IATDMCT recommendations specific to microsampling methods [1]. A clinical validation was performed by comparing plasma concentrations from venous blood (gold standard) to whole blood concentrations from venous blood using VAMS.

Results : The method was linear within 0.1 to 12 µg/mL. Within-day and between-day precisions and overall bias were within +/-15%. Relative matrix effect fulfilled the acceptance criteria.
Fluoroquinolones were stable in VAMS at RT at least 1 week and antivirals were stable at RT up to 8 hours after sampling and at least 1 weeks at -20°C or -80°C. No significant effect of the hematocrit was observed within the range of 0.20-0.60. Good correlation were found between the plasma concentrations and blood concentrations with coefficient of correlation between 0.97 and 0.99 in the clinical validation.
Discussion and conclusion : A LC-MS/MS method for the quantification of fluoroquinolones and antiviral drugs in whole blood using VAMS was developed and validated. This method will allow us to expand routine TDM of fluoroquinolones and antiviral drugs and implement it for at-home patients.

[1] Capiau, Sara et al. “Official International Association for Therapeutic Drug Monitoring and Clinical Toxicology Guideline: Development and Validation of Dried Blood Spot-Based Methods for Therapeutic Drug Monitoring.” Therapeutic drug monitoring vol. 41,4 (2019): 409-430.

Prevalence of Pharmacogenomic variables of Tacrolimus in patients of Renal Transplantation and their significance in Dose Requirement

Dr Smita Pattanaik[1], Ms Priyanka Naithani[1], Dr Deepesh Kenwar[1], Dr Savita Verma Atri[1], Mr Ajay Patial[1], Mr Sumit Dey[1], Ms Ritika Panwar[1], Ms Sheetal Singh[1], Dr Karthik V[1], Dr Shiva Kumar Patil[1], Dr Sarbpreet Singh[1], Dr Ashish Sharma[1]

[1]Post Graduate Institute of Medical Education And Research Chandigarh, Chandigarh, India

Immunosuppression 1, Sal D, september 25, 2023, 13:00 - 14:30

Introduction

Tacrolimus is the cornerstone of the immunosuppressant regimen in the treatment of patients of renal transplantation. Mutations in the cytochrome-P-450 enzyme (CYP) mainly CYP3A5, CYP3A4), their upstream regulators like Pregnene-X-receptor (PXR), Peroxisome Oxido-Reductase (POR), and drug efflux proteins ABCB1 confer differential dose requirement profiles in patients during the post-transplantation period. Though CYP3A5 has been identified as the major determinant of tacrolimus dose, the role of other pharmacogenomic determinants have not been explored in the Indian context. We performed this study, to gather the prevalence data and to understand, which of these SNPs should be considered for inclusion in the precision dosing of tacrolimus.

Material and methods

This was a prospective cohort study enrolling participants of renal transplant recipients from December 2017 to Jan 2020 (n=350). Five ml of blood sample was collected for genomic DNA extraction in EDTA vials in the pre transplantation period. The isolated DNA quality and purity was checked using a standard Nanodrop instrument and 50-100 nanogram (ng) of the DNA was used to perform the PCR with TaqMan pre-designed DME genotyping assay probes from ThermoFisher Scientific. We investigated the eight polymorphisms [CYP3A5*3, CYP3A4*1B, CYP3A4*22, ABCB1 1236 C>T, ABCB1 2677 C>T, ABCB1 3435 C>T, PXR(NR112), and POR*28]. The patients were followed up for at least one year for their drug dose titrations and clinical outcomes. The genotype mutation data were compiled for every patient according to their clinical profiles and tacrolimus trough concentration (C0).

Results

We observed a similar trend in CYP3A5 non-expressor (*3/*3) profile (54%) which is somewhat comparable to the previous study conducted in our centre in the year 2009 (61%) with RFLP genotyping. The frequency of the heterozygous allele, CYP3A4*1B (*1/*1B) was found to be 0.8% whereas we did not find any homozygous mutants (*1B/*1B). In contrast to the other parts of the world, we did not find any CYP3A4*22, variant in our study participants. In case of PXR(C>T), the frequency of the homozygous and heterozygous variant allele found in our study is 12.8% and 52%. For POR*28, we found 6% of the homozygous and 71.4% heterozygous. We also report a frequency of variant allele for ABCB1 1236 (C>T) as 28.5%, ABCB1 2677 (C>T) as 74% and ABCB1 3435 (C>T) as 41.7%. All the genotype frequencies were in accordance with Hardy Weinberg equilibrium. The penetration of the variant allele was markedly different for CYP3A5, POR, ABCB1 3435 and 2627. The dose requirement of tacrolimus was significantly influenced by the CYP3A5, POR and ABCB1 2627 status.

Discussion and conclusion

This is the first comprehensive study to report eight pharmacogenomic variants of tacrolimus disposition in a large cohort of patients with renal transplantation from India. CYP3A4 polymorphism does not appear to be important for precision dosing of tacrolimus, whereas POR has emerged as a significant factor especially when it is coupled with the CYP3A5 expressor status.

Detection of phosphatidylethanol in units of banked blood and its potential impact to interpretation of alcohol use.

Dr. Carmen Gherasim[1]
[1]University Of Michigan, Ann Arbor, United States

Clinical toxicology and drugs of misuse 1, Sal C, september 25, 2023, 13:00 - 14:30

Introduction: Phosphatidylethanol (PEth) is a specific biomarker for alcohol use with superior diagnostic values compared to traditional alcohol biomarkers including urinary ethyl glucuronide (uEtG), urinary ethyl sulfate (uEtS), and carbohydrate-deficient transferrin (CDT). Measurement of PEth concentration in the blood has become of increasing interest in a wide variety of clinical settings across United States including transplant evaluation, and monitoring alcohol use disorders due to the extended detection window of up to 28 days.
Objectives: To determine the concentrations of phosphatidylethanol in RBC units as a means to estimate the point prevalence of exposure within the healthy donor pool with potential implication to interpretation of alcohol use in transfused patients.
Methods: Segments from 100 RBC units were tested for the presence of PEth 16:0/18.1 using a laboratory developed liquid chromatography mass-spectrometry (LC-MS/MS) method on a Waters Acquity TQ-S instrument. PEth positivity was determined using a 20 ng/mL cutoff which represents the limit of quantification of our assay and is widely considered the cutoff concentration for light to moderate alcohol.
Results: Of the 44 (44%) units that contained Peth concentrations above 20 ng/mL, 34 (34%) units contained concentrations of 20-200 ng/mL consistent with moderate consumption of alcohol, and 8 (8.0 %) units contained concentrations >200 ng/mL consistent with heavy consumption. One RBC unit contained PEth levels >2,000 ng/mL consistent with binge drinking the day prior to blood donation.
Conclusions: Phosphatidylethanol is detectable within the US RBC supply. Further investigation is needed to determine the risks of transfusion-associated exposure to phosphatidylethanol in general patient populations as well as potential impact to interpretation of alcohol use in patients pre- and post- transplant monitored for alcohol use.

A novel method to quantify the microbiome-derived metabolism of mycophenolic acid in human fecal samples.

Master Of Science Ole Martin Drevland[1], PhD Eric J. de Muinck[3], PhD Anders Åsberg[1,2], MD, PhD Karsten Midtvedt[2], PhD Ida Robertsen[1]
[1]Department of Pharmacy, University Of Oslo, , Norway, [2]Department of Transplantation Medicine, Oslo University Hospital, , Norway, [3]Centre for Ecological and Evolutionary Synthesis, Department of Biosciences, University of Oslo,, , Norway

Immunosuppression 2, Sal D, september 26, 2023, 13:00 - 14:30

Introduction: A large part of the considerable interindividual variability in mycophenolic acid (MPA) pharmacokinetics remains unpredictable and unexplained. The gut microbiome interacts closely with drugs during the absorption phase and may be a significant source of variation in bioavailability. MPA undergoes extensive enterohepatic re-circulation, and the exposure of the secondary peak show large variability. Bacterial □-glucuronidase enzymes are central in this process as it converts the primary metabolite of MPA, mycophenolic acid glucuronide (MPAG), back to MPA in the intestine, which then is re-absorbed and increases systemic exposure of MPA and likely enhances immunosuppression and toxicity. The effect of interindividual differences in gut microbiota on this enterohepatic re-circulation and, thus, MPA dosing requirement is expected to be significant. The aim of this project was to develop a novel method for quantifying the microbiome dependent reactivation of MPA from MPAG and use the method to determine MPA reactivation rates in patient samples from renal transplant recipients and healthy volunteers.

Materials and Methods: To identify and quantify the effects of the gut microbiome on MPA pharmacokinetics, we developed our own in-house platform of in vitro fecal lysates, followed by UPLC-MS analysis for determination of the microbiome-derived metabolism of MPA. The developed method was applied to fecal samples from 12 healthy individuals in previously conducted clinical trials. Fecal lysates were prepared by using bead beating and sonication as cell lysis techniques. MPAG was added to the lysate and incubated for 2 hours. Samples for drug concentration measurements of MPA and MPAG were obtained every 15 to 30 minutes. Cumulative MPA concentration as a function of time was fitted to a linear regression function, with the slope representing the reactivation rate of MPA.

Results: Stability experiments have shown an MPAG recovery of 98% (□0.3%) after 24h, indicating low degree of unspecific deglucuronidation of MPAG. Adding amoxapine (inhibitor of the □-glucuronidase enzyme) to the fecal lysate further confirmed a high □-glucuronidase specificity of the method as a 5-fold decrease in the reactivation rate of MPA was shown. Preliminary results show MPA reactivation rates ranging between 15 and 19 nM/h in the samples obtained from the investigated individuals.

Discussions and Conclusions: We have developed a method that quantifies the depletion of MPAG and the reactivation of MPA in lysates prepared from fecal samples. The method will be applied to determine associations between MPA reactivation rates and in vivo MPA pharmacokinetics, together with the abundance of microbial composition, in patient samples.

The impact of immunological risk and tacrolimus variability on allograft rejection in pediatric liver transplantation

Guido Trezeguet Renatti[1,2], Julia Minetto[1], Agostina Arrigone[1], Cintia Yanina Marcos[1], Gabriela Aboud[1], Hayellen Reijenstein[1], Leandro Lauferman[1], Maria Florencia D'Arelli[1], Agustina Jacobo Dillon[1], Diego Aredes[1], Daniela Fernandez Souto[1], Gustavo Wildfeuer[1], Cecilia Gamba[1], Marcelo Dip[1], Oscar Imventarza[1], Esteban Halac[1], Paula Schaiquevich[1,2]
[1]Hospital Garrahan, , Argentina, [2]CONICET, , Argentina

Immunosuppression 1, Sal D, september 25, 2023, 13:00 - 14:30

The identification of risk factors for biopsy-proven acute rejection (BPAR) in pediatric liver transplantation is fundamental to reduce patient morbi-mortality(1-5). Previous studies at our center demonstrated the impact of tacrolimus variability on the risk of developing BPAR (6). We also identified HLA-DQ eplet mismatch (eMM) as risk factor for BPAR in preliminary studies, but the importance of other immunological variables such as the presence of donor-specific antibodies (DSA) has been elusive in liver transplantation. Our aim was to evaluate the correlation between HLA eMM, tacrolimus variability and DSA as risk factors for BPAR. Patients transplanted between 2018 and 2021 were included and prospectively followed. Donor/recipient pairs were HLA-typed by NGS and the eMM was quantified using the HLAMatchmaker version of HLA Fusion software 4.6. Tacrolimus variability was calculated as the CV% and tortuosity, and the percentage of tacrolimus C0 determinations <5 ng/mL was calculated for each patient. DSA was evaluated from available serum using LIFECODES Single Antigen Assays. Demographic, clinical, and pharmacological covariates were included in univariate ($p<0.2$) and Cox multivariate models. For variables retained in the multivariate model, the cohort was categorized according to the thresholds obtained by ROC analysis. Chi-squared test was performed to compare the proportion of patients that developed BPAR according to the presence of DSA. Sixty-six of the 167 liver transplant patients recruited since 2018 had full available data and were on tacrolimus as primary immunosuppression. Median (range) age at transplant was 1.3 years (0.5-17.4). BPAR-free survival at 1 and 2 years post-transplant was 68.1% (95%CI, 57.4-80.8) and 58.7% (95%CI, 47.3-72.8), respectively. Eleven of the 51 patients with available post-transplant data developed DSA: 8 anti-HLA class II, 2 anti-HLA class I, and 1 patient developed anti-HLA class I and II antibodies. Tacrolimus tortuosity (HR 11.50, 95%CI, 4.53-28.98; $p<0.001$) and HLA-DQ antibody verified (ab) eMM (HR 1.20, 95%CI, 1.02-1.41; $p=0.025$) were identified as independent risk factors for BPAR. Even though the most frequent DSA observed was anti-HLA DQ (n=6), no significant association was found between the presence of anti-HLA-DQ antibodies and BPAR development. Having a tacrolimus tortuosity≥1.06 (sensitivity 73.7%, specificity 64.3%; AUC=0.73) and HLA-DQ ab eMM≥5 (sensitivity 94.7%, specificity 28.6%; AUC=0.60) was considered high tortuosity and high HLA-DQ ab eMM. In this large cohort of patients, we emphasize the role of tacrolimus variability and immunological risk as factors associated with BPAR. Further studies are ongoing to assess the role of DSA on BPAR and liver fibrosis.

Isobaric interferences by drug metabolites in liquid chromatography-tandem mass spectrometric methods (LC-MS/MS): A case with a pipamperone metabolite

PhD Christoph Schöberl[1], Sina Junger[1], Nicole Erlacher[2], Alexandra Voss[1], Kevin Wanek[1], Dr. med. Eberhard Wieland[1], Maria Shipkova[1]
[1]Competence Center for Therapeutic Drug Monitoring, MVZ Leinfelden-Echterdingen GmbH, Synlab Holding Germany GmbH, Leinfelden-Echterdingen, Germany, [2]Vitos Clinic for Forensic Psychiatry Haina, Vitos GmbH, Haina, Germany

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction: Isobaric interference between haloperidol and pipamperone in LC-MSMS methods based on the shared m/z transitions 376.1/165.1 and 376.1/123.1 is well known. Measures to overcome it are for example chromatographic separation of the two molecules or applying the m/z of another haloperidol isotope for quantification. In contrast to pipamperone the haloperidol molecule includes a chlorine atom that results in a high manifestation of the isotope 37Cl transitions 378.1/165.1 and 378.1/123.1 allowing both for sufficient LLOQ and shorter analytical run time with the second approach. Here we report about a newly identified case of interference by a pipamperone metabolite that can still compromise the measurement.
Materials and Methods: To explore the source of a persistent mass signal with m/z of the 37Cl isotop in our haloperidol method for more than a month after switching of the therapy of a patient from haloperidol to pipamperone following experiments were performed: a) samples from different patients (n=13) sent to the laboratory for pipamperone analysis were run with the haloperidol method as well as with a screening method covering >5000 different drugs and metabolites (Toxtyper®, Bruker Daltonics Inc. Bremen, Germany equipped with the Maurer / Wissenbach / Weber LC-MSn Library of Drugs, Poisons, and Their Metabolites, 2nd Edition); b) external quality assurance samples (EQAS, n=6) that included both pipamperone and haloperidol but no metabolites were analyzed separately by the pipamperone and haloperidol methods and the results were compared with the respective target concentrations. Methods used for the experiments (separate LC-MS/MS methods for pipamperone and haloperidol and ion-trap LC-MSn for the screening) were fully validated and accredited for the use in routine analytics.
Results: Both pipamperone and haloperidol concentrations measured in the EQAS samples met the respective EQUAs criteria without any evidence of interferences. “Haloperidol” signals ranging between 1.0 – 12.2 µg/L were detected in the pipamperone patient samples. The respective pipamperone concentrations ranged between 13.8 - 395 µg/L and correlated to the “haloperidol” signals (Spearman’s Rho: 0.945; $p<0.05$). However, no haloperidol or haloperidol metabolites were identified with the Toxtyper®-screening method in these samples. In contrast numerous pipamperone metabolites were detected including a metabolite dihydropipamperone with a mass spectrum including m/z 378.1/165.1 and 378.1/123.1. Extending the haloperidol MS-method with an additional mass transition (378.1/293.1) characteristic for this metabolite but not for haloperidol before repeating the analysis, confirmed interference by the metabolite.
Discussion and Conclusions: A new isobaric interference in a haloperidol LC-MS/MS method caused by the pipamperone metabolite dihydropipamperone was identified and described. The interference can be avoided e.g. by improved LC separation. The case demonstrates the importance of including native patient samples containing both drugs and their metabolites in method validation protocols.

Comparison of LC-MS and a Benzodiazepine Immunoassay in Urine Samples to Assess Compliance in Poly Drug Abusers Undergoing a Detoxification Program with Oxazepam.

Prof. Dr. Eberhard Wieland[1], Sonja Martin[1], PD Dr. Maria Shipkova[1]
[1]Synlab Medical Center Leinfelden-Echterdingen, Leinfelden-Echterdingen, Germany

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction: Detoxification is the safe and effective discontinuation of a substance of dependence or misuse. The goals of detoxification treatments are to minimize any withdrawal effects and alleviate any side effects.

Material and Methods: We have followed 33 polydrug abusers (age 22-51 Y) in a detoxification program replacing uncontrolled drug use by administration of oxazepam in a controlled manner. To assess compliance urine screens were performed by an immunoassay (IA) for benzodiazepines (Syva Emit II Plus Benzodizepine Assay, Siemens, Germany) and a semiquantitative in-house LC-MS/MS method for oxazepam established on a Waters H-Class UPLC XEVO TQD instrument. In addition, an initial toxicological screen was performed using the Toxtyper ion trap instrument (Bruker, Germany). Semiquantitative results of the immunological screen and LC-MS/MS were normalized to the urine creatinine after hydrolysis with glucuronidase. Oxazepam was prescribed at decreasing doses starting with 120 mg/day. Patients were followed up until cessation of oxazepam administration.

Results: In all urine samples collected at the start of therapy benzodiazepines were detected (oxazepam (n=33), diazepam (n=29), nordiazepam (n=24), temazepam (n=31), alprazolam (n=2), alpha hydroxy alprazolam (n=2), lorazepam (n=6), bromazepam (n=2), flunitrazepam (n=1)). Accordingly, all urine screens with the IA were positive. After starting the detoxification therapy only a weak overall correlation (r=0.38) was observed between signals in the IA and the oxazepam doses. The overall correlation was better between the LC-MS/MS results and the oxazepam dose (r=0.61). The correlation between the signals of the IA and LC-MS/MS was also poor (r=0.481). When comparing the correlation between dose and signals in the IA as well as in the LC-MS/MS just within the first 10 days the correlation to the dose was worse (r=0,24 for IA and r=0,45 for LC-MS/MS) compared to measurements after day 10 (r=0,45 for IA and r=0,67 for LC-MS/MS).

Discussions and Conclusions: The results show in general a poor correlation between the oxazepam dose and the signals in a urine benzodiazepine immunoassay. Even with a more specific analysis of oxazepam using LC-MS/MS the correlation between dose and signal was modest. Correlation coefficients between the oxazepam dose improved beyond day 10 when most of the initially present benzodiazepines were eliminated and oxazepam was the predominant benzodiazepine present in the urine samples. Immunoassay screens cross reacting to various benzodiazepines should not be used to assess compliance to oxazepam detoxification particularly not in the early phase when a mixture of benzodiazepines and metabolites can be expected.

Blood ammonia level was rarely correlated to the serum valproate concentration: a retrospective analysis of real-world data

MD Jiyeon Park[1], MD Ki Young Huh[1], MD, PhD SeungHwan Lee[1], MD, PhD Jae Yong Chung[2], MD, PhD In Jin Jang[1], MD, PhD Jae Seong Oh[1]
[1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, , South Korea, [2]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Bundang Hospital, Seongnam, , South Korea

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction
Monitoring of blood ammonia levels is recommended while using valproate to prevent valproate-induced hyperammonemic encephalopathy. However, the risk factors and clinical significance of valproate-induced hyperammonemia are not clear yet. The aim of this study was to evaluate the relationship between blood ammonia level and serum valproate concentration, and the following valproate dose adjustment decision by analyzing real-world therapeutic drug monitoring (TDM) data.

Materials and Methods
Patients' electrical medical data who underwent valproate TDM from 2002 to 2022 at Seoul National University Hospital were extracted from the clinical data warehouse system without personal information. The following data were reviewed and analyzed: serum valproate trough concentrations and blood ammonia levels which were measured on the same day; the patient's valproate dosing history; and so on. The result of valproate TDM was classified into three groups (dose increased, dose not changed, and dose decreased). The relationship between the blood ammonia level and serum valproate concentration was analyzed using the linear mixed effect model. Also, the following result of dose decreased or not was analyzed on the blood ammonia level using the generalized linear mixed model.

Results
A total of 11,507 valproate TDM cases from the 3,685 patients' data were evaluated. The mean [min-max] value of the valproate and ammonia concentration was 64.41 [1.6-194.2] μg/mL and 79.07 [7 - 964] μg/dL. The percentage of patients with hyperammonemia (> 100 μg/dL) was 20.2%. The estimate of the fixed effect (serum valproate concentration) was 0.0429 with a 0.015 standard error, which rarely explained the ammonia level. The number of cases and the average blood ammonia level of the three groups (dose-increased, dose not changed, and dose decreased) were as follows: 2,047 cases (78.08 μg/dL), 7,703 cases (79.07 μg/dL), and 1,757 cases (79.94 μg/dL) respectively. The estimate of the fixed effect (blood ammonia level) was -0.0023 with a 0.0001 standard error, which scarcely explained the result of whether the following valproate dose decreased or not.

Discussions and Conclusions
The elevation of blood ammonia levels is often reported in patients who are taking valproate. In this study, we showed that the blood ammonia level was rarely explained by the serum valproate concentration through real-world data analysis. Even in some hyperammonemic patients, the dose of valproate was not decreased. The clinical efficacy of valproate might have been prioritized over the risk of hyperammonemia, especially if there is no symptom of encephalopathy. Further research to elucidate the risk factors of hyperammonemic encephalopathy when using valproic acid is needed.

Clinical Implementation of DPYD Genotyping Test for Guiding Fluoropyrimidine Therapy

Dr. Lei Fu[1,2], Betty Wong[1], Michael Jonathon Raphael[1,2], Carlo De Angelis[1,2], Weei-Yuarn Huang[1,2], David Hwang[1,2]
[1]Sunnybrook Health Sciences Centre, Toronto, Canada, [2]University of Toronto, Toronto, Canada
Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Lei Fu1,4,5, Betty Wong1, Michael Jonathon Raphael2,4,6, Carlo De Angelis3,4, Weei-Yuarn Huang1,5, and David Hwang1,4,5

1Precision Diagnostics and Therapeutics Program (Laboratory Medicine), Sunnybrook Health Sciences Centre, 2Departments of Medical Oncology, and 3Pharmacy, Sunnybrook Odette Cancer Centre, 4Sunnybrook Research Institute, 5Departments of Laboratory Medicine and Pathobiology, and 6Medicine, University of Toronto, Toronto, ON, Canada

Abstract:

Fluoropyrimidines, such as 5-fluorouracil (5-FU) and capecitabine, are widely used for patients with solid tumors, and are the chemotherapy backbone in colorectal and other gastrointestinal chemotherapy regimens. It has been reported that as many as 10-30% patients treated with fluoropyrimidine drugs experience severe toxicity. The DPYD gene encodes the rate-limiting enzyme dihydropyrimidine dehydrogenase (DPD) responsible for fluoropyrimidine catabolism. The US Food and Drug Administration (FDA) added warning statements to the drug labels for 5-FU to against its use in patients with DPD deficiency. Since 2017, the Clinical Pharmacogenetics Implementation Consortium (CPIC) has updated its practice guideline for DPYD genotype and fluoropyrimidine dosing. Recently, Cancer Care Ontario announced its intention to fund DPYD genotype testing in patients receiving fluoropyrimidine chemotherapy.

In response to the clinical needs, our laboratory has developed an allele specific PCR method for DPYD genotyping. The variants included in testing panel are c.557A>G (p.Y186C, rs115232898), c.1129-5923C>G (rs75017182), c.1679T>G (p.I560S, rs55886062), c.1905+1G>A (rs3918290) and c.2846A>T (p.D949V, rs67376798). The accuracy of the method has been confirmed by Sanger sequencing. This assay has been validated according to clinical laboratory quality standards and received regulatory approval. Since its clinical implementation in the past five months, nearly one hundred patients have been tested. Four patients were identified as heterozygous carriers for one of the variants, enabling the fluoropyrimidine dose in these patients to be adjusted according to the CPIC guideline.

In conclusion, our genotyping assay has been proven to be accurate and robust in detecting the five most common variants in DPYD gene. The genotype results will help improve patient safety by enabling more personalized dosing for fluoropyrimidine chemotherapy regimens.

A Retrospective Quality Review of Vancomycin Target Attainment in a Haematology Ward at a University Hospital in Sweden

Pharmacist Emelie Lefvert[1], Pharmacist Maria Swartling[2], PhD Anna-Karin Hamberg[2,3], PhD Elisabeth Nielsen[2]
[1]Uppsala University Hospital, UPPSALA, Sverige, [2]Department of Pharmacy, Uppsala University, UPPSALA, Sverige, [3]Division of Clinical Pharmacology, Uppsala University Hospital, UPPSALA, Sverige

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction: Vancomycin is commonly used to treat infections in patients with malignant diseases since they have a severely impaired immune system after receiving cytotoxic drugs. The patients also have an increased risk for acute kidney injury (AKI) due to predisposed exposures and susceptibilities associated with non-specific AKI. Since vancomycin has a narrow therapeutic window, therapeutic drug monitoring (TDM) is recommended to ensure adequate treatment effect without adverse drug reactions, including AKI.
Material and methods: A retrospective observational study was performed at the Haematology ward at Uppsala University Hospital, Sweden. Clinical data from 2019-2021 were extracted from the electronic medical record system. The extent of measured trough concentrations, model estimated trough concentrations as well as model derived daily area under the curve (AUC24h) that were within the recommended target range for vancomycin (15-20 mg/L and 400-600 mg*h/L, respectively), were examined. The occurrence of AKI (definition by KDIGO) during vancomycin treatment was also investigated. Quality of TDM-sampling times were assessed by observing discrepancies between documented and actual TDM-sampling times during January and February 2022.
Results and discussion: 305 trough concentrations of vancomycin were registered from 72 treatment cycles in 62 patients. 65.2% of the model derived AUCs were within the target range. Of the measured trough concentrations and estimated trough concentration were only 43.6% and 48.2%, respectively, within the recommended target. Of the estimated AUCs, 9.5% were subtherapeutic and 25.2% were supratherapeutic. From the measured and estimated trough concentrations, 31.8% and 36.4% were subtherapeutic, whereas 24.6% and 15.4% were supratherapeutic, respectively. The differences in measured and estimated trough concentrations could be explained by deviations in the sampling time. The TDM-samples were on average taken 47 minutes before the actual trough concentration whereas the estimated trough concentrations represented true troughs. As dose adjustments in current clinical practice are based on measured trough concentrations there is a risk of misinterpreting the TDM-results, giving patients suboptimal dose recommendations. Regardless of the patients' kidney function at start of treatment, AKI stage 1-3 occurred in 27.8% of the vancomycin treatment cycles. Observation of sampling time showed a mean discrepancy of 8 minutes between actual and documented sampling time.
Conclusion: A majority of the measured and estimated trough concentrations were outside of the therapeutic target for vancomycin. Even though 65,2 % of the AUCs were within the therapeutic window there is room for improvement for patients treated with vancomycin at the Hematology ward in Uppsala. Out of the given treatment cycles, 27.8% gave some degree of AKI. The small discrepancy between documented and actual sampling times creates good conditions for using model informed precision dosing for vancomycin in this vulnerable patient group with several other risk factors for AKI.

Optimal sample times for monitoring quetiapine extended release.

Azucena Aldaz[1], PhD Maria del Mar Unceta[1], Pharm D Carmen Barace, PhD Patricio Molero
[1]Clínica Universidad De Navarra, Pamplona, Spain

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

1.Introduction
Therapeutic drug monitoring of quetiapine extended release (XR) refers to the fact that the samples can be taken in the morning (mid-interval) since this concentration is expected to be twice than trough levels. This statement is based, mainly, on the study by Figueroa (2009) belonging to the trading company. In clinical practice, we have not observed this.

2. Materials and Methods
57 patients diagnosed with schizophrenia (n=12) and bipolar depression (n=45), were recruited, between January 2020 and December 2022. They were 25 men and 32 women. 26 patients received quetiapine immediate release (IR) and 31 extended release (XR), which are the ones studied. In 8 patients with the XR formulation, blood was withdrawn in the morning and prior to the dose in the evening. Serum concentrations of quetiapine (QTP) and its active metabolite norquetiapine (N-QTP) were analyzed by UPLC-MS/MS. XR doses ranged from 150 to 600 mg daily.
3.Results
Morning mean ± SD values for XR QTP and N-QTP were 250.3±226.9 ng/mL and 200.8±161.05 ng/mL, respectively. In the samples taken in the afternoon, before taking, the respective results were 28.5±22.5 ng/mL and 140.0±83.0 ng/mL. The N-QTP/QTP ratios were 1±0.86 (morning) and 6.76±3.63 (evening)
4. Discussions and Conclusions
In the morning extraction, the QTP concentrations, when using the XR formulation, are 778.4% higher than the evening values, much higher values than the widespread belief (100%). The N-QTP/QTP ratios are significantly different between morning and evening, which can lead to errors in the interpretation of the response because according to some researchers the best responses are obtained at high values of this ratio

Finger-prick sampling for the monitoring of tacrolimus, creatinine and hemoglobin in kidney transplant recipients: Assessment of self-sampling and healthcare professional-performed sampling with two volumetric devices

MScPharm, PhD Nils Tore Vethe[1], MScPharm, PhD Anders Åsberg[5], BSc Anders M. Andersen[1], MD, PhD Ragnhild Heier Skauby[3], MScPharm, PhD Stein Bergan[4], MD, PhD Karsten Midtvedt[2]
[1]Department of Pharmacology, Oslo University Hospital, Oslo, Norway, [2]Department of Transplantation Medicine, Oslo University Hospital, Oslo, Norway, [3]Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway, [4]Department of Pharmacology, Oslo University Hospital and Department of Pharmacy, University of Oslo, Oslo, Norway, [5]Department of Transplantation Medicine, Oslo University Hospital and Department of Pharmacy, University of Oslo, Oslo, Norway

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction:
Following kidney transplantation, self-collection of blood samples may enable a more convenient and flexible outpatient follow-up. Additionally, the concept may save resources for the healthcare system. Volumetric capillary (finger-prick) sampling emerges as an attractive tool for therapeutic drug monitoring and associated diagnostics. Currently there are knowledge gaps regarding how finger-prick self-sampling performs compared with assisted finger-prick sampling by healthcare professionals. In the present study, we aimed to assess the clinical performance (total error) of using two volumetric devices (Capitainer®qDBS and Mitra®) for monitoring tacrolimus, creatinine and hemoglobin in kidney transplant (KTx) recipients.

Materials and Methods:
We compared finger-prick and venous sampling in three settings: microsampling performed by healthcare personnel, self-sampling under supervision, and unsupervised self-sampling. The two microsampling devices studied were Capitainer® qDBS 10 µL (Capitainer AB, Solna, Sweden) and Mitra® 10 µL (Trajan Scientific and Medical, Melbourne, Australia). Finger-prick samples were collected at 3 time-points; before tacrolimus dosing in the morning (t0), one hour and three hours after dosing (t1 and t3). Capitainer 2×10 µL and Mitra 2×10 µL were obtained at all sampling time points. We collected liquid venous blood samples close in time to all microsamples, except at t1 and t3 in the unsupervised self-sampling situation. The finger-prick samples were analyzed with adapted methods and the results compared to routine method analysis of the venous blood samples. Tacrolimus area under the concentration versus time curve (AUC) was predicted with a Bayesian forecasting model.

Results:
Twenty-five KTx recipients (age 21-74 years) completed the study. For measurement of tacrolimus at single time points and predicted AUC, the proportions within ±20% difference were 79-96% for Capitainer and 77-95% for Mitra. For creatinine, the correction algorithms x(estimated) = (y-5.0) / 0.83 and x(estimated) = (y-4.4) / 0.93 was derived and applied for Capitainer and Mitra. The proportions within ±15% of creatinine in liquid blood plasma were 92-100% for Capitainer and 79-96% for Mitra. For hemoglobin, the correction factor 1.134 was used for Capitainer and 1.102 for Mitra. Proportions within ±15% of hemoglobin in liquid blood samples were 100% for Capitainer and 67-92% for Mitra. Comparing sampling situations, the success rate was consistent for Capitainer (92-96%), whereas Mitra showed success rate of 72-88% with samples collected by healthcare professionals and 52-72% when collected by the patients themselves.

Discussions and Conclusions:

We found that tacrolimus trough concentration and predicted AUC can be reliably monitored with both sampling devices, provided that the microsamples are technically qualified upon arrival in the laboratory. Creatinine and hemoglobin could be reliably monitored when both types of microsamples were collected by trained healthcare professionals, but only Capitainer showed the same reliability with self-collected samples under our study conditions. Implementing volumetric finger-prick self-sampling for the monitoring of tacrolimus, creatinine and hemoglobin is feasible and may simplify and improve the follow-up of kidney transplant recipients.

Pharmacogenomics of tramadol in Japanese orthopedic surgery patients

Dr Tomohiro Terada[1], Dr Takaki Kamiya[2], Dr Daiki Hira[1], Dr Ryo Nakajima[3], Ms Kazuha Shinoda[4], Ms Atsuko Motomochi[2], Ms Aya Morikouchi[2], Dr Yoshito Ikeda[2], Dr Tetsuichiro Isono[2], Mr Michiya Akabane[2], Dr Satoshi Ueshima[4], Dr Shinji Imai[3], Dr Mikio Kakumoto[4]
[1]Department of Clinical Pharmacology and Therapeutics, Kyoto University Hospital, Kyoto, Japan, [2]Department of Pharmacy, Shiga University of Medical Science Hospital, Otsu, Japan, [3]Department of Orthopaedic Surgery, Shiga University of Medical Science, Otsu, Japan, [4]College of Pharmaceutical Sciences, Ritsumeikan University, Kusatsu, Japan

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

[Introduction] Pharmacogenomic (PGx) testing can predict therapeutic responses or adverse effects based on genetic variants and is expected to be an effective clinical test for precision medicine patient management. Tramadol is an orally available, centrally acting, weak-opioid analgesic drug, which is metabolized by the cytochrome P450 (CYP) 2D6 enzyme to its primary active metabolite O-desmethyl tramadol via O-demethylation. This study aimed to investigate the impact of the CYP2D6 genotype on the analgesic effect of tramadol in real-world clinical practice.
[Materials and Methods] A retrospective cohort study was conducted in patients treated with tramadol for postoperative pain after arthroscopic surgery for rotator cuff injury from April 2017 to March 2019. The impact of the CYP2D6 genotype on the analgesic effects assessed by numeric rate scale (NRS) is analyzed by the Mann-Whitney U test. Stepwise multiple linear regression analysis was performed to identify predictive factors for the area under the time- NRS curve (NRS-AUC) calculated using the linear trapezoidal method.
[Results] Among 85 enrolled Japanese patients, the number of phenotypes with CYP2D6 normal metabolizer (NM), and intermediate metabolizer (IM) was 69 (81.1%) and 16 (18.9%). There is no ultra-rapid metabolizer (UM) and poor metabolizer (PM) in this study population. The NRS and NRS-AUC of the IM group were significantly higher than those in the NM group until Day 7 ($P < 0.05$). In addition, average daily dose of co-prescribed celecoxib in Day15-28 in IM group was significantly higher than NM group. The multiple linear regression analysis indicated that the CYP2D6 polymorphism was a predictive factor of the high level NRS-AUC in Day 0-7. Even when variable factors, such as sex and age, were considered, these results suggested that CYP2D6 genotype testing is a reliable predictable biomarker of analgesic effect of tramadol.
[Conclusion] In IM patients, analgesic effect of tramadol significantly decreases after Orthopedic surgery in the real-world clinical practice. Therefore, the dose escalation of tramadol or changing the analgesic were recommended for IM patients.

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Adalimumab serum levels and anti-drug antibodies: associations to treatment response and drug survival in inflammatory arthritis patients

Md, Phd Student Ingrid Jyssum[1,2], MD, PhD Johanna Elin Gehin[3], PhD Joseph Sexton[1], MD, PhD Eirik K Kristianslund[1], MD, PhD Yi Hu[4], PhD David J Warren[3], MD, PhD, Professor Tore K Kvien[1,2], MD, PhD, Professor Espen A Haavardsholm[1,2], MD, PhD Silje Watterdal Syversen[1], MD, PhD Nils Bolstad[3], MD, PhD Guro Løvik Goll[1]

[1]Center for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, Oslo, Norway, [2]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway, [3]Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway, [4]Lillehammer Hospital for Rheumatic Diseases, Lillehammer, Norway

Biologicals, Sal B, september 26, 2023, 13:00 - 14:30

Objectives

The aim of this study was to explore associations between serum adalimumab level, treatment response and drug survival in order to identify a therapeutic range. Also, to assess occurence of, and factors associated with anti-drug antibodies (ADAb).

Methods

We measured serum adalimumab and ADAb levels by using automated fluorescence assays and registered 3-month treatment response in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) or spondyloarthritis (SpA) starting adalimumab. Therapeutic ranges were suggested based on concentration-effect analyses. Logistic regression was used to explore factors associated with ADAb.

Results

In 340 included patients (97 RA, 69 PsA, 174 SpA), the median adalimumab level at 3 months was 7.3 mg/L (IQR 4.0 to 10.3) and 33 (10%) patients developed ADAb, with findings comparable across diagnosis. In RA and PsA, adalimumab levels ≥ 6 mg/L was associated with treatment response at 3 months (Odds Ratio [OR] 2.2 [95% CI 1.0, 4.4]) and less drug discontinuation (Hazard Ratio [HR] 0.49 [0.27, 0.80]). Drug levels ≥ 12 mg/L showed no additional benefit. In SpA, a therapeutic range could not be identified, but the likelihood for response to therapy increased with higher adalimumab levels (OR for response 1.2 [95% CI 1.02, 1.3]).

Higher occurence of ADAb formation and lower drug levels were seen with previous bDMARD use, no methotrexate comedication and in treatment with adalimumab-Humira compared to adalimumab-Hyrimoz.

Conclusion

Higher adalimumab levels were associated with improved drug survival and clinical response. The suggested therapeutic range of adalimumab is 6-12 mg/L for RA/PsA. In SpA, a therapeutic range could not be detected.

A comparative analysis of therapeutic drug monitoring (TDM) implementation in Greece in the last 20 years

Prof Vangelis Manolopoulos[1,2], Ms Gavriela Voulgaridou[1], Ms Theodora Paraskeva[1], Ms Natalia Atzemian[1], Konstantina Portokallidou[1,2], Dr Georgia Ragia[1], Prof George Kolios[1,2], Dr Konstantinos Arvanitidis[1,2]

[1]Laboratory of Pharmacology, Individualized Medicine and Pharmacological Research Solutions (IMPReS) Center,Democritus University of Thrace Medical School, Alexandroupolis, Greece, [2]Clinical Pharmacology Unit, Academic General Hospital of Alexandroupolis, Alexandroupolis, Greece

Miscellaneous 1, Møterom 2, september 26, 2023, 13:00 - 14:30

Introduction: TDM is the long-established clinical practice of measuring drug concentrations. It can be used to determine treatment efficacy and prevent the occurrence or reduce the risk of drug-induced side effects, being, thus, a tool of personalized medicine. This study aims to quantify implementation of TDM in Greek hospitals and present the trends and progress of TDM in the country over the last 20 years.

Materials and Methods: All Greek public hospitals were invited to provide data and details on the clinical uptake of TDM in Greece for the years 2002 and 2021 through a structured questionnaire. Data were collected from 113 out of 132 Greek hospitals in 2002, whereas in 2021, we collected data from 98 out of 122 Greek hospitals. All data are presented as mean±SD.

Results: In 2002 and 2021, 64 and 51 hospitals, respectively, performed TDM. The total number of drug measurement assays decreased from 2002 to 2021 by almost 41% (153,313±7,793.8 vs. 90,065±5,697.9; p=0.043). Antiepileptics and antibiotics were the most common drug categories monitored in both years. Although the total number of antiepileptic drugs was almost reduced by half in 2021 (49190 versus 21250), they remain the main category of drugs measured in Greek hospitals. Vancomycin is the most common antibiotic requested for TDM, measured in almost all hospitals measuring antibiotics. In hospitals where TDM was performed both in 2002 and 2021 (n=35), a decrease in measurements is present for carbamazepine (198.8±46.6 vs. 46.6±10.1; p<0.001), phenytoin (253.6±59 vs. 120±34.3; p=0.001), tobramycin (16±7 vs. 0.57±0.6; p=0.017), amikacin (147.3±65.2 vs. 91.1±71.4; p=0.033), digoxin (783. 2±226.70 vs. 165.9±28.9; p<0.001), and theophylline (71.5±28.7 vs. 11.9±6.4; p=0.004) throughout the years, while only for vancomycin an increase in measurements is recorded (206.1±96.1 vs. 789.1±282.8; p=0.012).

Discussion and Conclusion: This is a seminal study conducted to evaluate the current TDM situation in Greece and compare the progress of TDM in Greek public hospitals over the last 20 years. Our results show that TDM has declined through the years in Greek hospitals. This happens despite the fact that guidelines for TDM implementation in several drug categories or specific drugs are constantly increasing. Some of the drugs for which TDM is not being implemented in Greece are biological agents, antiretroviral drugs, beta-lactams, and neuropsychological drugs. Clinical pharmacologists should increase their efforts in understanding the reasons for this decline and helping in overturning it by further promoting to all stakeholders the benefits of TDM for patients and the health system.

Funding: This study was financially supported by Grant MIS 5047189 (Establishment of a Center of Excellence for Pharmacological Studies and Precision Medicine – IMPReS), under the Operational Program “Competitiveness, Entrepreneurship and Innovation” (NSRF 2014–2020), co-financed by Greece and the European Union.

In vivo protein binding investigation of first-line antituberculosis drugs

Mr David Fage[1], Prof. Frédéric Cotton[1]
[1]Laboratoire Hospitalier Universitaire De Bruxelles – Universitair Laboratorium Brussel (LHUB-ULB), Brussels, Belgium

Anti-infectives 2 - antibiotics and antifungals, Møterom 4, september 26, 2023, 13:00 - 14:30

Introduction
Data from tuberculosis patients about the effect of hypoalbuminemia, sepsis or altered renal function on the first-line antituberculosis drugs binding are missing. Thus, the main purposes of this study were first to investigate thoroughly the relation between the carrier-proteins level and the drug binding and second to investigate the feasibility of predicting the free drug concentrations.

Materials and methods
LC-MS/MS method. Our previously published method (doi.org/10.1016/j.jpba.2022.114776) allowed the simultaneous quantification of the four first-line drugs as well as five second-line drugs with an isotopologue standard for each drug. It was further validated to quantify the free drug concentrations (Cfree measured).
Drug binding. The drugs protein binding was explored by an ultrafiltration device after validation against microdialysis (gold standard).
Population. The study was performed on remaining plasma from clinical samples of drug-susceptible tuberculosis patients received for TDM purpose (n=18).
Biochemical tests. Total protein, albumin, α1-acid glycoprotein, C-reactive protein and creatinine were measured with Roche kits on Cobas Instruments.
Statistical analysis. The correlations were estimated using the Spearman coefficient (rs). The free drug concentration was calculated (Cfree predicted) based on the median binding of the drug or the binding normalized to the albumin level. The agreement between Cfree measured and Cfree predicted was characterized by the root mean square error (RMSE).

Results
We measured a median protein binding of 1.5% for ethambutol (n=45), 9.7% for isoniazid (n=42) and 0.7% for pyrazinamide (n=43) among an albumin range of 21-45 g/L. Their bindings were not related to the total drug concentration (Ctotal), the total proteins level, the C-reactive protein value or the renal function (rs<0.270; p-value >0.05). As other first-line drugs, rifampicin binding (n=48) was not related to the C-reactive protein value or the renal function. The impact of the albumin level on the rifampicin binding showed two different patterns depending on the albumin range. Above 30 g/L of albumin, the median binding of 88.7% was characterized by a low variability of its range of measure [82.3-96.0] and not related to Ctotal (rs=0.024 [-0.311-0.354]; p-value >0.05) or the albumin level (rs=0.236 [-0.105-0.527]; p-value >0.05) (n = 37). The prediction of Cfree showed an excellent accuracy (RMSE=0.3413). Below 30 g/L of albumin, we observed a median binding of 78.8% [51.6-88.9] with a drastic fall of the binding in the samples from the severe hypoalbuminemia patient (21 g/L) (n = 11). In this situation, the mathematical prediction of Cfree was inaccurate (RMSE= 1.1443).

Discussion and conclusions
The determination of Cfree seemed to have few interest for ethambutol, isoniazid, and pyrazinamide due to their low protein binding but a major one for rifampicin in case of hypoalbuminemia where its Ctotal was an inaccurate reflection of Cfree. In this case, Cfree should be measured. Further investigations should be carried out to investigate the clinical benefit of measuring Cfree for rifampicin, especially in the critical period of active tuberculosis associated to hypoalbuminemia.

In vitro protein binding investigation of second-line antituberculosis drugs

Mr David Fage[1], Prof. Frédéric Cotton[1]
[1]Laboratoire Hospitalier Universitaire De Bruxelles – Universitair Laboratorium Brussel (LHUB-ULB), Brussels, Belgium

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction
Data about antituberculosis drugs binding are lacking for second-line drugs that are used extensively for multi-drug resistant tuberculosis (MDR-TB) (moxifloxacin, levofloxacin and linezolid). Thus, the main purposes of this study were first to investigate thoroughly the relation between the carrier-proteins level and the drug binding and second to investigate the feasibility of predicting the free drug concentrations.

Materials and methods
LC-MS/MS method. Our previously published method (doi.org/10.1016/j.jpba.2022.114776) allowed the simultaneous quantification of the four first-line drugs as well as five second-line drugs with an isotopologue standard for each drug. It was further validated to quantify the free drug concentrations (Cfree measured). Only bedaquiline could not be quantified in other matrices than plasma.
Drugs binding. The drugs protein binding was explored by an ultrafiltration device after validation against microdialysis (gold standard). In vitro experiments mimicked real-case samples by spiking drugs combinations from the clinical practice. The MDR-TB regimen included [bedaquiline/fluoroquinolone/linezolid/clofazimine] where the fluoroquinolone was moxifloxacin (n=24) or levofloxacin (n=32) and the high-level isoniazid resistance drug-susceptible TB regimen was levofloxacin/rifampicin/ethambutol/pyrazinamide] (n=15). The drugs concentration and the albumin level were spread over a wide range of values to explore the protein binding.
Biochemical tests. Total protein, albumin and α1-acid glycoprotein were measured with Roche kits on Cobas Instruments.
Statistical analysis. The correlations were estimated using the Spearman coefficient (rs). The free drug concentration was calculated (Cfree predicted) based on the median binding of the drug or the binding normalized to the albumin level. The agreement between Cfree measured and Cfree predicted was characterized by the root mean square error (RMSE).

Results
We measured a median protein binding of 26.2% for levofloxacin, 12.8% for linezolid and 46.3% for moxifloxacin among a wide albumin range [19-48 g/L]. The correlation between the binding and the albumin level was strong for linezolid (rs=0.732 [0.570-0.839]; p-value <0.0001), very strong for levofloxacin (rs=0.900 [0.816-0.947]; p-value <0.0001) and was characterized by a linear relationship through the whole albumin range. The model to predict Cfree was accurate for linezolid (RMSE=0.5632) and levofloxacin (RMSE=0.3250) if the binding was normalized to the albumin level. Moxifloxacin binding had a moderate association with albumin level (rs=0.540 [0.162-0.779]; p-value=0.0065) and Ctotal (rs=-0.532 [-0.122 to -0.775]; p-value=0.0074) with a wide confidence interval. The prediction of Cfree based on the median binding showed an excellent accuracy (RMSE=0.3664) and a direct relation between Ctotal and Cfree.

Discussion and conclusion
Despite the relation with the albumin level, the determination of Cfree seemed to have few interest for moxifloxacin because Ctotal was an acceptable reflection of Cfree and a limited interest for linezolid due to its low binding. For levofloxacin, Ctotal was an inaccurate reflection of Cfree due to the important impact of the albumin level on the binding. Cfree could be accurately predicted for levofloxacin making the measurement of Cfree potentially unnecessary. Based on these preliminary

results, further investigations should be carried out to investigate in vivo the interest of Cfree and the feasibility of its prediction.

Performance Evaluation of an Automated Assay for Measurement of Everolimus* on the Atellica® Solution Immunoassay Analyzer

Dr Sarah Baxter[1], Mr Nigel Casson[1], Mrs Clare Murray[1], Ms Louise Hanson[1], Mr Tom Chuang[2]
[1]Randox Laboratories Ltd., Crumlin, United Kingdom, [2]Siemens Healtineers, Tarrytown, United States of America

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction: Everolimus is utilised as an immunosuppressant to prevent rejection in solid organ transplants. At the cellular level, Everolimus binds to the intracellular FK506-binding protein (FKBP12), which subsequently binds to mTOR complex, inhibiting downstream IL-2 signal transduction. The correlation between steady-state trough concentration and area under curve (AUC) provides reliable therapeutic monitoring for Everolimus exposure at the trough level. Randox Laboratories have developed a new Everolimus Immunoassay, which is dedicated for use on the Atellica® Solution Immunoassay Analyzer. The objective of this study was to determine the performance characteristics of the Everolimus Assay on the Atellica® Immunoassay Analyzer.
Method: The Atellica® Everolimus Assay is a competitive immunoassay using direct chemiluminescent technology. Everolimus in the patient sample competes with bound Everolimus in the solid phase for binding with the acridinium ester-labeled anti-everolimus antibody. The Everolimus concentration in the sample is inversely proportional to the amount of Relative Light Units measured by the Analyzer. EDTA whole blood specimens are pre-treated prior to analysis using a convenient 'vortex-go' method.
Performance characteristics of the assay, including precision, linearity, limit of blank, limit of detection, limit of quantification, interfering substances, and method comparison, were determined using three reagent lots on the Atellica® instrument, according to CLSI guidance. One hundred ninety-seven EDTA whole-blood samples from a combination of kidney, liver, and cardiac transplant patients with Everolimus concentrations ranging from 2.2 to 30.2 ng/mL were tested using the Atellica® Everolimus Assay and the ADVIA Centaur XP Everolimus assay which is directly traceable to the LC-MS/MS Everolimus method from Sydpath (Sydney, Australia). The relationship between methods was analyzed using Passing-Bablok regression. Interference studies comprised a panel of endogenous substances, metabolites, and potentially co-administered drugs, tested at a concentration of approximately 3 times cMAX.
Results: The Atellica® Everolimus Assay demonstrated a mean %CV of 3.02% for intra-assay and 5.61% for total precision (spanning a sample range of 3.17 to 29.59 ng/mL). LoB, LoD, and LoQ were 0.15 ng/mL, 0.35 ng/mL, and 1.26 ng/mL, respectively. Linearity was demonstrated from LoQ to 30 ng/mL. A panel of 86 potential interferents including those listed below were tested and found not to interfere (≤10%): acyclovir to 100 µg/mL, amphotericin B to100 µg/mL, cyclosporin A to 2 µg/mL, erythromycin to 20 mg/dL, phenobarbital to 150 µg/mL, tacrolimus to 0.12 µg/mL, sulfamethoxazole to 400 µg/mL, tobramycin to 100 µg/mL, trimethoprim to 50 µg/mL, bilirubin (conjugated) to 60 mg/dL, bilirubin (direct) to 60 mg/dL, and rheumatoid factor to 1350 IU/mL. Close correlation to the ADVIA Centaur XP was demonstrated, with an r, slope, and intercept of 0.991, 1.1, and 1.31, respectively.
Conclusion: The resulting data demonstrates that the Atellica® Everolimus Assay is an accurate and precise method of quantifying Everolimus concentration in EDTA whole-blood samples.
*Assay under development by Randox Laboratories Ltd. for Siemens Healthineers. Not currently available for sale.

Performance Evaluation of an Automated Assay for Measurement of Tacrolimus* on the Atellica® Solution Immunoassay Analyzer

Dr Sarah Baxter[1], Mr Ross Swan[1], Ms Oliwia Sankiewicz[1], Mr Nigel Casson[1], Mr Tom Chuang[2]
[1]Randox Laboratories Ltd., Crumlin, United Kingdom, [2]Siemens Healthineers, Tarrytown, United States of America

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction: Tacrolimus (FK506) (PROGRAF®) is utilised as an immunosuppressant to prevent rejection in solid organ transplants. Tacrolimus is a macrolide antibiotic of fungal origin (Streptomyces tsukubaensis) which inhibits calcineurin, a phosphatase which activates T cell proliferation. At the cellular level, Tacrolimus binds a family of binding proteins termed FKBPs (FK506 binding proteins). The correlation between steady-state trough concentration and area under curve (AUC) provides reliable therapeutic monitoring for Tacrolimus exposure at the trough level. Randox Laboratories have developed a new Tacrolimus Immunoassay, which is dedicated for use on the Atellica® Solution Immunoassay Analyzer. The objective of this study was to determine the performance characteristics of the Tacrolimus Assay on the Atellica® Immunoassay Analyzer.
Method: The Atellica® Tacrolimus Assay is a competitive immunoassay using direct chemiluminescent technology. Tacrolimus in the patient sample competes with the bound tacrolimus in the solid phase for binding with the acridinium ester-labeled anti-tacrolimus antibody. EDTA whole blood specimens are pre-treated prior to analysis using a convenient 'vortex-go' method.
Performance characteristics of the assay, including precision, linearity, limit of blank, limit of detection, limit of quantification, interfering substances, and method comparison, were determined using three reagent lots on the Atellica® instrument, according to CLSI guidance. One hundred eleven EDTA whole-blood samples from kidney transplant patients with tacrolimus concentrations ranging from 2.3 to 23.2 ng/mL were tested using the Atellica® Tacrolimus Assay and the ADVIA Centaur XP Tacrolimus assay which is directly traceable to the LC-MS/MS Tacrolimus method from Analytical Sciences International (UK). The relationship between methods was analyzed using Passing-Bablok regression. Interference studies comprised a panel of endogenous substances, metabolites, and potentially co-administered drugs, tested at a concentration of approximately 3 times cMAX.
Results: The Atellica® Tacrolimus Assay demonstrated a mean %CV of 2.48% for intra-assay and 3.81% for total precision (spanning a sample range of 2.74 to 27.13 ng/mL). LoB, LoD, and LoQ were 0.38ng/mL, 0.78 ng/mL, and 1.93 ng/mL, respectively. Linearity was demonstrated from LoQ to 30 ng/mL. A panel of 86 potential interferents including those listed below were tested and found not to interfere (≤10%): acyclovir to 6.6 mg/dL, amphotericin B to100 µg/mL, cephalosporin to 100 µg/mL, erythromycin to 13.8 mg/dL, phenobarbital to 10 mg/dL, rapamycin to 5 µg/mL, sulfamethoxazole to 150 µg/mL, tobramycin to 3.3 mg/dL, trimethoprim to 4.2 mg/dL, bilirubin (conjugated) to 60 mg/dL, bilirubin (direct) to 60 mg/dL, and rheumatoid factor to 500 IU/mL. Close correlation to the ADVIA Centaur XP was demonstrated, with an r, slope, and intercept of 0.964, 1.09, and -0.508, respectively.
Conclusion: The resulting data demonstrates that the Atellica® Tacrolimus Assay is an accurate and precise method of quantifying tacrolimus concentration in EDTA whole-blood samples.
*Assay under development by Randox Laboratories Ltd. for Siemens Healthineers. Not currently available for sale.

Performance Evaluation of an Automated Assay for Measurement of Sirolimus* on the Atellica® Solution Immunoassay Analyzer

Dr Sarah Baxter[1], Mr Nigel Casson[1], Mrs Clare Murray[1], Ms Louise Hanson[1], Mr Tom Chuang[1]
[1]Randox Laboratories Ltd., Crumlin, United Kingdom, [2]Siemens Healthineers, Tarrytown, United States of America

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction: Sirolimus is utilised for the prophylactic treatment of acute rejection in renal transplant patients. The therapeutic range of Sirolimus is quite narrow, and it is therefore essential that the drug concentration is monitored accurately to prevent potential adverse events. Randox Laboratories have developed a new Sirolimus Immunoassay, which is dedicated for use on the Atellica® Solution Immunoassay Analyzer. The objective of this study was to determine the performance characteristics of the Sirolimus Assay on the Atellica® Immunoassay Analyzer.
Method: The Atellica® Sirolimus Assay is a competitive immunoassay using direct chemiluminescent technology. Sirolimus in the patient sample competes with bound Sirolimus in the solid phase for binding with the acridinium ester-labeled anti-sirolimus antibody. The Sirolimus concentration in the sample is inversely proportional to the amount of Relative Light Units measured by the Analyzer. EDTA whole blood specimens are pre-treated prior to analysis using a convenient 'vortex-go' method. Performance characteristics of the assay, including precision, linearity, limit of blank, limit of detection, limit of quantification, interfering substances, and method comparison, were determined using three reagent lots on the Atellica® instrument, according to CLSI guidance. One hundred twenty-four EDTA whole-blood samples from kidney transplant patients with Sirolimus concentrations ranging from 2.04 to 23.09 ng/mL were tested using the Atellica® Sirolimus Assay and the ADVIA Centaur XP Sirolimus assay which is directly traceable to the Abbot Alinity Sirolimus Immunoassay. The relationship between methods was analyzed using Passing-Bablok regression. Interference studies comprised a panel of endogenous substances, metabolites, and potentially co-administered drugs, tested at a concentration of approximately 3 times cMAX.
Results: The Atellica® Sirolimus Assay demonstrated a mean %CV of 2.85% for intra-assay and 5.58% for total precision (spanning a sample range of 3.72 to 22.95 ng/mL). LoB, LoD, and LoQ were 0 ng/mL, 0.26 ng/mL, and 1.59 ng/mL, respectively. Linearity was demonstrated from LoQ to 30 ng/mL. A panel of 114 potential interferents including those listed below were tested and found not to interfere (≤10%): acyclovir to 1000 µg/mL, amphotericin B to100 µg/mL, cyclosporin A to 2 µg/mL, erythromycin to 20 mg/dL, phenobarbital to 150 µg/mL, tacrolimus to 0.12 µg/mL, sulfamethoxazole to 400 µg/mL, tobramycin to 100 µg/mL, trimethoprim to 50 µg/mL, bilirubin (conjugated) to 60 mg/dL, bilirubin (direct) to 60 mg/dL, and rheumatoid factor to 1350 IU/mL. Close correlation to the ADVIA Centaur XP was demonstrated, with an r, slope, and intercept of 0.996, 1.02, and 1.51, respectively.
Conclusion: The resulting data demonstrates that the Atellica® Sirolimus Assay is an accurate and precise method of quantifying Sirolimus concentration in EDTA whole-blood samples.
*Assay under development by Randox Laboratories Ltd. for Siemens Healthineers. Not currently available for sale.

Ultra-fast, Accurate and Simultaneous Quantification of Ritonavir and Lopinavir in Human Plasma

Mr Aymeric Morla[1], Mr Mats Garmer[1], Mr Rahul Baghla, Mr Rolf Kern
[1]Sciex, , France

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

INTRODUCTION:
Protease inhibitors (PIs) are a class of anti-viral drugs that prevent viral replication by selectively binding to viral proteases and inhibiting their function. The development of PI-based therapies has been of enormous benefit to people infected with HIV. Unfortunately, the effectiveness of protease inhibitors can fade over time. Mutations during viral replication can result in viruses that produce new, different proteases that are not targeted by current PI therapies. The best way to avoid this drug resistance is to reduce or stop HIV replication. With less HIV replication, there is less of a chance of a new strain that is resistant to antiHIV drugs. To keep HIV levels as low as possible, PIs are typically taken in combination with at least two other anti-HIV drugs. Such combination therapies are referred to as highly active antiretroviral therapy (HAART). Lopinavir and ritonavir are two protease inhibitors that are often used as part of a fixed-dose combination, and serve as the model compounds in this study.

OBJECTIVE:
To develop a method utilizing Acoustic Ejection Mass Spectrometry (AEMS), as implemented in the Echo® MS System with a SCIEX Triple Quad™ 6500+ LCMS/MS system, which offers clear benefits for quantification of lopinavir and ritonavir in human plasma. Requiring minimal sample preparation and no chromatographic separation, it provides high sample throughput without sacrificing robustness or reproducibility.

METHODS:
Lopinavir and ritonavir were spiked into human plasma samples in the range of 0.5 ng/mL to 250 ng/mL each. Samples were processed using a liquid-liquid extraction method and 0.4 mL of supernatant liquid was collected and dried under a nitrogen stream. Samples were reconstituted in 100 µL of 25% v/v methanol in water and transferred to a 384-well plate for analysis by AEMS. Methanol with 0.1% v/v formic acid was used as carrier solvent at a flow rate of 425 µL/min in the AEMS with 50 nL sample volumes. MS/MS detection was performed using the SCIEX Triple Quad 6500+ LC-MS/MS.

RESULTS:
Calibration curves, along with quality control samples, all analyzed in six replicates, demonstrated the high reproducibility of AEMS when combined with liquid-liquid extraction. Excellent %CVs were achieved across all concentration levels with no interference in blank human plasma samples. Even at the extremely short analysis time of 3 seconds per sample, the method yielded LLOQs of 0.5 ng/mL for both lopinavir and ritonavir. The assay accuracy was 85.31–112.34% for ritonavir and 85.51–113.52% for lopinavir. The calibration curve covered approximately 3 orders of magnitude (0.5–250 ng/mL) for both analytes and displayed linearity (r2) of 0.9934 for ritonavir and 0.9946 for lopinavir using a weighting of 1/x2.

CONCLUSION:
The Echo® MS System produced very sensitive, accurate and reproducible results for the simultaneous quantitative analysis of lopinavir and ritonavir in human plasma. Having a very short analysis time (3 sec/sample) enabled rapid generation of quantitative data for high numbers of samples, and with the assay showing great reproducibility even without using labeled internal standards. Future use of labeled internal standards is recommended to further improve these results.

Model-informed infliximab dosing and clearance monitoring of a patient with acute severe ulcerative colitis

Dr. Zhigang Wang[1], Dr. Wannee Kantasirpitak[1], Dr. Debby Thomas[1], Dr. Prof. João Sabino[2,3], Dr. Prof. Marc Ferrante[2,3], Dr. Prof. Bram Verstockt[2,3], Dr. Prof. Séverine Vermeire[2,3], Dr. Prof. Erwin Dreesen[1]
[1]University of Leuven, Department of Pharmaceutical and Pharmacological Sciences, Leuven, Belgium, [2]University of Leuven, Department of Chronic Diseases and Metabolism, Leuven, Belgium, [3]University Hospitals Leuven, Department of Gastroenterology and Hepatology, Leuven, Belgium

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Background
Accelerated infliximab (IFX) clearance is associated with treatment failure in patients with acute severe ulcerative colitis (ASUC).[1] We hypothesise that model-informed precision dosing (MIPD) can guarantee adequate IFX exposure and disease control.

Methods
A multi-model selection algorithm was used to evaluate dosing and probability of target attainment (PTA) in a patient with ASUC. [2] The patient's pharmacokinetics (PK) parameters were predicted using Bayesian forecasting (BF) based on measured IFX serum trough concentrations (TCs). Dose selection aimed at ≥80% probability of maintaining serum IFX ≥30 mg/L up to day (d)14, ≥15 mg/L between d15 and d42, and to target the area under the IFX concentration-time curve from start of therapy to d84 (AUCd0-d84) ≥3750 mg×d/L.[3]

Results
A 60-kg patient with ASUC received a first 10 mg/kg IFX infusion at d0 and a 5 mg/kg infusion at d14. On d34, a first serum sample was taken right before giving 10 mg/kg IFX (eight days earlier than usual). The measured d34 IFX TC of 11.0 mg/L was below the 15 mg/L target. BF with the d34 TC predicted IFX PK parameters corresponding to a terminal half-life of 14.8 days. Simulation of the patient's IFX concentration-time course predicted a 0.0% PTA at d14 (predicted TC range 15.9-29.4 mg/L). Without any further IFX infusions, the AUCd0-d84 was predicted to be 3071 mg×d/L (95% PI 2791-3362 mg×d/L; 0.0% PTA). Thus, a 10 mg/kg IFX infusion was given four weeks later (d64), which was predicted to result in a AUCd0-d84 of 4118 mg×d/L (95% PI 3793-4452 mg×d/L; 98.0% PTA). A serum sample was taken right before the d64 infusion. IFX PK parameters were again updated using BF with the measured d64 TC of 3.3 mg/L, now predicting a AUCd0-d84 of 4327 mg×d/L (95% PI 3844-4739 mg×d/L; 99.6% PTA) .
IFX treatment was continued with 10 mg/kg doses every four-to-six weeks. Patient-reported outcomes remained stable (stool frequency 2, rectal bleeding 0) up to d192 (most recent hospital visit). A total of 2085 mg IFX (133% more than standard 5 mg/kg at weeks 0, 2, 6) was given to the patient during induction.
Covariate-based predictions (not using IFX TC) underestimated the IFX clearance (0.288 L/d) and terminal half-life (19.0 days).

Conclusion
BF with our multi-model algorithm using IFX concentrations can facilitate clearance monitoring and precision dosing of IFX in patients with ASUC. Covariate-based predictions are not reliable. AUC-targeted dosing may not be feasible with routine TDM, but can be easily implemented with a user-friendly MIPD software tool.

References
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Infliximab clearance predicts the risk of relapse during maintenance treatment of patients with inflammatory bowel disease

Dr. Zhigang Wang[1], Dr. Prof. Niels Vande Casteele[2], Dr. Prof. Marc Ferrante[3,4], Dr. Prof. Séverine Vermeire[3,4], Dr. Prof. Erwin Dreesen[1]
[1]Department of Pharmaceutical and Pharmacological Sciences, University of Leuven, Leuven, Belgium, [2]Department of Medicine, University of California San Diego, San Diego, Belgium, [3]Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium, [4]Department of Chronic Diseases and Metabolism, University of Leuven, Leuven, Belgium
Biologicals, Sal B, september 26, 2023, 13:00 - 14:30

Background:
Therapeutic drug monitoring (TDM) of intravenously administered infliximab is common practice in patients with inflammatory bowel disease (IBD). However, infliximab concentrations do not only drive response, but they are also driven by disease activity (e.g. increased infliximab clearance due to leakage through the inflamed bowel wall). This bi-directional relation between pharmacokinetics (PK) and pharmacodynamics (PD) may undermine the clinical impact of TDM as adequate exposure in the presence of high infliximab clearance may still result in poor outcomes. This study aimed to disentangle the bi-directional PK-PD relationship of infliximab and investigate the potential benefit of clearance monitoring over concentration monitoring.

Methods:
Data from 189 patients (the TAXIT trial: 65 ulcerative colitis [UC], 124 Crohn's disease [CD]) who underwent infliximab dose optimisation based on clinical features (n=78) or TDM (n=101) were included. All filtered patients were in steroid-free combined clinical and biological remission at the start of the study and remission was systematically evaluated at each hospital visit over one year. Time-to-relapse was modelled using a parametric repeated time-to-event (RTTE) model. Various hazard functions (exponential, Weibull, Gompertz, Surge) were explored. Time-varying covariates as well as baseline covariates were investigated as predictors of the relapse hazard risk. Infliximab clearance was calculated using weighted averaging of the Bayesian forecasted estimates of four population PK models coded in NONMEM. [1]

Results:
Of all patients, 49.7% (n=27 [UC]; n=67 [CD]) experienced at least one relapse event during the year following start of dose optimisation, with up to four and nine relapse events for patients with UC and CD, respectively. An exponential hazard model best described the relapse data of patients with UC, with a constant baseline hazard of 0.00519 day-1 (RSE=9.7%). The Gompertz hazard model best described the data of patients with CD, with the baseline relapse hazard increasing over time from 0.00519 day-1 at inclusion to 0.0162 day-1 at one year (hazard ratio [HR]=3.12; 95% CI [2.30-4.24]). The infliximab TC did not have a significant impact on the relapse hazard risk (P>0.05). However, the infliximab clearance had a significant impact on the baseline hazard (dOFV 16.4 points). An increase in estimated infliximab clearance from 0.371 (25th percentile) to 0.561 (75th percentile) L/day was associated with an HR of 1.38 (95% CI [1.15-1.66]). An increase in measured CRP from 1.40 (25th percentile) to 12.8 (75th percentile) mg/L was associated with an HR of 2.24 (95% CI [1.84-2.71]). The functions of the two final hazard models are presented below:
UC: H(t)=0.00519*e^((1.7*(clearance-0.453)+0.0706*(CRP-4.7)))
CD: H(t)=0.00519*e^((1.7*(clearance-0.453)+0.0706*(CRP-4.7)))*e^((0.00312*time))

Conclusion:
We developed an RTTE model that demonstrated a significant association between higher infliximab clearance and increased risk of relapse in patients with IBD. While infliximab TCs lose their predictive ability for remission when doses are optimised, infliximab clearance remains a relevant predictor of

remission. This also explains why patients with adequate exposure still lose response. Our infliximab clearance monitoring software tool can provide valuable information to forecast the risk of relapse when patients with IBD are on TDM.

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Correlation between AUC of Mycophenolate Mofetil and its gastrointestinal tolerability in renal transplant recipients

Ms Priyanka Naithani[1], Dr. Smita Pattanaik[1], Dr. Ashish Sharma[2], Ms. Ritika Panwar[1], Ms. Sheetal Singh[1], Mr. Sumit Dey[3], Ms. Neeru Sharma[1], Dr. Shiva Patil[2], Dr. Sarabpreet Singh[2], Dr. Deepesh B. Kenwar[2]

[1]Department of Pharmacology, Postgraduate Institute Of Medical Education And Research, Chandigarh, chandigarh, India, [2]Department of Renal Transplant Surgery, Postgraduate institute of medical education and research, Chandigarh, Chandigarh, India, [3]Department of Urology, Postgraduate institute of medical education and research, Chandigarh, Chandigarh, India

Immunosuppression 2, Sal D, september 26, 2023, 13:00 - 14:30

Background: The introduction of MMF in the immunosuppressive regimen has led to a significant reduction in the incidence of acute rejection, although its use is associated with an increased rate of gastrointestinal complications. Gastrointestinal complications have a wide clinical spectrum, varying from idiopathic non-infective diarrhea to post-transplant inflammatory bowel disease (IBD). Diarrhea is a frequent but overlooked complication in renal transplantation, often considered by patients and clinicians, an unavoidable side effect of immunosuppressive regimens. However, it is associated with a significant impairment in life quality. Severe and chronic post-transplant diarrhea may lead to dehydration, malabsorption, rehospitalization, immunosuppression, noncompliance, and a greater risk of graft loss and death. However, it is not clear whether it is due to increased drug and/or metabolite exposure or related to specific mycophenolate formulation.

Methods: The study was undertaken with the aim of determining a correlation between the exposure of MPA and MPAG (measured by a limited AUC) and its association with chronic diarrhea (diagnosed as possibly drug related) in renal transplant recipients. This was conducted as a prospective observational study. enrolled 30 patients with complains of long-standing diarrhea (>2weeks) with all stool workup being negative for bacteria, viral and parasitic causes. These patients also did not respond completely for dose reduction of mycophenolate, use of probiotics and were therapeutic range for calcineurin inhibitors. The control group included 10 patients who never complained of diarrhea since transplantation. All the participants were on MMF and underwent sampling at time points 0, 1, 2, 4 and 6 hours after administration of a dose of MMF. The exposure was determined by calculation of the area under the plasma concentration-time curve (AUC) for MPA and MPAG.

Results: Out of 30 patients 23 (76.6%) were male and 7 (23.3%) were female patients. The mean age was 36.9±10years. The mean BMI was 20±4. Out of 30 patients 74% patients were from the emotionally related living donor group while 26% were from the cadaveric group. 2/30 were on CsA and 28/30 were on tacrolimus in the diarrhea group whereas all recipients were in tacrolimus in control group. The mean AUC (0-12) of MPA in the diarrhea group was 67.05±44.14 ug*hr/ml whereas, in the control group it was 91.78±55 ug*hr/ml and the p value is 0.24. The mean AUC(0-12) of MPAG in the diarrhea group was 380.56±125.97ug*hr/ml whereas, in the control group it was 369.74±152.62 ug*hr/ml and the p value is 0.84. There was a huge variation in the AUC of MPA (45.1 to 188) in diarrhea group as well as control group (42.4 to 215.04). Similarly, the AUC of MPAG (190 to 613) in diarrhea group as well as control group (130.8 to 482.86)
Conclusion: Our data does suggest that there is high inter-individual variation the concentration of MPAG and MPA achieved in patients with GI intolerance as well as those who did not. Our study results also indicate that exposure to MPA and MPAG are not predictive of this adverse event and therefore, exploration of other risk factors should be considered.

Role of uracil and dihydrouracil (DHU) to predict serious adverse events with 5-Fluorouracil in patients with malignancy

Dr Binu Susan Mathew[1], Dr Ajoy Oommen John[1], Dr Poornima Sivamani[1], Dr Ashish Singh[1], Dr Sumith K Mathew[1], Dr Gowri Mahasampath[1], Dr Anjana Joel[1], Dr Ratna Prabha[1], Dr Raju Titus Chacko[1]
[1]Christian Medical College Vellore, Vellore, India

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

Introduction

The adverse event outcome with 5-fluorouracil (5-FU) is associated with partial or complete deficiency of dihydropyrimidine dehydrogenase (DPD) enzyme which metabolizes > 80% of 5-FU to its inactive metabolite. The ideal screening strategy to identify those with DPD deficiency has conflicting opinion, between phenotyping, genotyping or multiparametric approach. In this phenotype approach, uracil (U) and the ratio of dihydrouracil/uracil (DHU/U) was measured and correlated with serious adverse events (SAE) ≥ Grade 3 after 5-FU.

Material and Methods

This prospective observational study was done in patients prior to initiating 5-FU. Demographic details were collected on the day of the study. Blood sample was collected between 8.00 - 9.00 am from patients after an overnight fast for phenotype testing and transported in ice. Within ten minutes of collection, plasma was separated and stored in -80 ℃ till analysis of uracil and DHU, as based on our earlier published literature. After the 5-FU therapy was completed, SAE were noted from the hospital records. Correlation between the phenotype levels and SAE were studied.

Results

58 males and 21 females were recruited with a mean (SD) age, weight and height of 47 (14) yrs, 61.2 (12.7) kg and 162.8 (9.4) cm respectively. Malignancies ranged from gastrointestinal (n,72) to head and neck (n,7). The 5-FU regimens (n) included FOLFOX (45), FOLFIRINOX (8), FOLFIRI (3), FLOT (10), mDCF (9) and infusional 5-FU (3) and with trastuzumab (1). The median (IQR) of uracil and DHU was 7.8 (5.8, 10.8) and 117.5 (92, 131) ng/ml respectively and of the ratio DHU/uracil was 14.4 (10.6, 17.8). SAE ≥ Grade 3 (n) were recorded as follows: Death (2), myocardial infarction-MI (3), hand foot syndrome -HFS (3), neuropathy (3), mucositis (4), diarrhoea (6), febrile neutropenia (4), thrombocytopenia (7), neutropenia (14 and anaemia (17).

In simple logistic regression, uracil level was identified as a significant predictor of ≥ Grade 3 hematological toxicity (p = 0.037) which included either severe anaemia (p=.001), neutropenia (p=0.42) or thrombocytopenia. DHU/U ratio also significantly predicted severe anaemia (p=.002). Uracil levels demonstrated a trend towards prediction of any SAE ≥ Grade 3 which included hematological toxicity, diarrhoea, neuropathy, mucositis, hand foot syndrome, myocardial infarction and death [Odds ratio, 95%CI: 1.13 (0.99, 1.3)]. All the three patients who had uracil >16 ng/ml developed ≥ Grade 3 SAE and had a ratio of <9. Of the 3 patients with HFS, 2 had uracil ≥14, and two of the three with MI had uracil ≥12. With lower cut-off values, for uracil ≥12 and ratio of ≤11, 71% and 65% developed ≥ Grade 3 adverse events respectively.

Discussion and Conclusion

Measurement of uracil and ratio of DHU/uracil has a role to predict the development of one or more haematological adverse events ≥ Grade 3. Of the patients who had the literature recommended cut-off for uracil >16 ng/ml, all developed a severe SAE. The correct threshold cut-off for uracil and ratio in this population to predict ≥ Grade 3 SAE is yet to be identified with a study in a larger cohort.

TDM of antiseizure medication through quantitative DBS

Doctor Chiara Cancellerini[1], Doctor Erika Esposito[1], Doctor Alice Caravelli[1], Doctor Martina Soldà[1], Doctor Luca Vignatelli[1], Professor Francesca Bisulli[1], Doctor Laura Licchetta[1], Professor Jessica Fiori[2]
[1]IRCCS Istituto delle Scienze Neurologiche di Bologna, Full Member of the European Reference Network for Rare and Complex Epilepsies (EpiCARE), Bologna, Italy, Italy, [2]Department of Chemistry "G. Ciamician", University of Bologna, Bologna, Italy, Italy

Alternative sampling strategies 2, Møterom 1, september 26, 2023, 13:00 - 14:30

Background:
Therapeutic Drug Monitoring (TDM) of Antiseizure Medications (ASMs) is an essential tool for persons with epilepsy (PWE) follow-up, aimed to optimize individual drug therapy. Venipuncture is the reference-standard method for TDM, but it requires high-volume blood taken by skilled nurses and can be difficult to perform in pediatric or uncooperative PWE(1,2). Microsampling is increasingly proposed as a clinically practical and reliable sampling methodology for TDM. Compared with traditional venous blood collection, it allows to collection a lower blood volume through a less painful and invasive fingerprick. Dried Blood Spot (DBS) was adopted since the 1960s as a microsampling technique that allows remote sampling, meaning that patients are not required to travel to a hospital. Despite the many advantages of DBS, this method was associated with a lack of volumetric control and the well-described hematocrit (HCT) effect. Among these, quantitative Dried Blood Spot (qDBS, Capitainer®-Sweden) are proposed as free to over-sampling and HCT-induced inaccuracies(3). There are currently no other studies using qDBS devices for TDM of ASMs. A few articles presented an extraction method for different drugs and biomarkers (3,4,5) The study's aim was to validate the extraction method of ASMs in the Capitainer®-qDBS (10 µL).

Methods:
According to EMA guidelines, for the quantification of ASMs from Capitainer®-qDBS device by Ultra-High Liquid Chromatography-Tandem Mass Spectrometry (UHPLC-MS/MS), extraction technical validation was done(6). Four ASMs were included in the analysis: Carbamazepine (CBZ), Lacosamide (LCS), Levetiracetam (LEV) and Lamotrigine (LTG). Different extraction solvents were tested for protein precipitation as Acetonitrile, Methanol, Methanol/Ethanol (1:1), Acetonitrile/0.1% Formic Acid, Methanol/0.1% Formic Acid, Methanol/Ethanol/0.1% Formic Acid.
Bland Altman analysis and Passing Bablok regression between ASMs concentration found in Capitainer®-qDBS collected with left-over venous blood patient and plasma samples were done.

Results:
The method was proved to be accurate and precise using Acetonitrile as chosen extraction solvent. Indeed, intra-assay and inter-assay reproducibility analyses showed accuracy and precision ≤15% over a calibration range from 0,4 to 15 µg/ml for CBZ, 0,5-10 µg/ml for LCS, 0,5-20 µg/ml for LTG and 1-80 µg/ml for LEV. Recovery was found >85 % and the matrix effect was found <10% for all ASMs. The stability was tested at 7, 14 and 30 days of storage, at room temperature and -20°C. Blood to plasma ratio was found and used to convert Capitainer®-qDBS results. A preliminary statistical analysis through Bland Altman and Passing Bablok regression showed a linear correlation for all the ASMs.

Conclusions:
To our knowledge, this is the first study considering Capitainer®-qDBS application for ASMs quantification. A new UHPLC-MS/MS method to measure ASMs concentration in capillary blood samples collected by Capitainer®-qDBS was developed and validated according to EMA guidelines criteria(4).Capitainer®-qDBS sampling provides a simple and accurate technique to collect capillary blood and offers the benefits to overcome the classical DBS technique. Further studies are needed to validate this capillary fingerprick method on a wider number of ASMs and to assess the clinical applicability in real-life settings.

Keywords: therapeutic drug monitoring, dried blood spot, antiseizure medications, ultrahigh liquid chromatography-tandem-mass spectrometry, qDBS.

Vincristine pharmacokinetics in patients with malignant lymphoma

MD, PhD Ragnhild Heier Skauby[1], BSc Anders Mikal Andersen[2], MSc, Pharm, PhD Nils Tore Vethe[2], MSc, Pharm, PhD Stein Bergan[2,3]
[1]Department of Medical Biochemistry, Oslo University Hospital , Oslo, Norway, [2]Department of Pharmacology, Oslo University Hospital, Oslo, Norway, [3]Department of Pharmacy, the University of Oslo, Norway, Oslo, Norway

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction:
Neurotoxicity is a major challenge following chemotherapy treatment in cancer patients. Patients treated with vincristine (VCR) are particularly susceptible for these side effects. Symptoms and findings of VCR neurotoxicity vary greatly among patients, and may differ from paresthesia and modest loss of sensibility to chronic neuropathic pain, distinct ataxia and paresis. Dosing of VCR is usually based on clinical assessments. Adverse effects often elicit a dose reduction, which may lead to sub-optimal treatment. Given the large inter- and intra-individual pharmacokinetic variability displayed by VCR, TDM may be a valuable tool for individualizing and optimizing VCR therapy, with the aim of reducing VCR doses without compromising efficacy.

The objective of the main study was to observe the development of peripheral neuropathy in patients with malignant lymphoma. The study included 50 patients (age 18-75 years), diagnosed with Hodgkin's and non-Hodgkin's lymphoma, receiving CHOP regimen (vincristine sulfate, prednisolone, cyclophosphamide, doxorubicin hydrochloride) as chemotherapy treatment.

As a substudy, we wanted to characterize the pharmacokinetics of VCR in patients with malignant lymphoma, and to investigate if VCR may be a candidate suitable for TDM. Furthermore, correlations with adverse effects due to VCR (primarily peripheral neuropathy) will be investigated.

Materials and Methods:
During week 1 and 4 of the CHOP regimen, venous blood samples were collected at predose (C0), and approximately after 1, 2, 4 , 6, 24, 48 and 72 hours after dosing. Plasma was separated and stored at -80◦C until analysis. All samples were analyzed for total concentrations of VCR using an in-house developed HPLC-MSxMS method, and the pharmacokinetic profiles (area under the plasma concentration vs time curves, AUC) were analyzed.

Sample preparation was based on protein precipitation and direct injection of a 10 µL aliquot from the supernatant. The blood plasma sample volume was 125 µL. The HPLC-MS/MS analytical instrumentation was a Transcend II LX-2 ultra-HPLC-system coupled to a TSQ Quantiva mass spectrometer (Thermo Fisher Scientific, Waltham, MA). Chromatographic separation was performed at room temperature (23-25 °C) on Raptor Biphenyl columns (30 x ID 3.0 mm, particle size 5 µm; Restek). The chromatographic run-time per injection was 2 minutes and 8 seconds. The measurement range of the assay was 0.020 -10.40 µg/L. The between-runs coefficient of variation (CV) was <9%.

Results:
Preliminary results from seven patients dose intervals during the first week of the CHOP regimen (all values given as median and range):

An almost four-fold difference in AUC0-24 between patients was observed, as the analysis of the dose intervals showed an AUC0-24 of 9.7 (5.8–20.4) µg*h/L. Peak concentration (Cmax) was 0.99 (0.57–2.88) µg/L, showing a five-fold range. For three of the patients, percentage change in AUC0-24 from the first to the fourth week of the CHOP regimen was 1, 7 and 49% respectively.

Discussion and conclusions:
Evidence to demonstrate a relationship between VCR exposure and VCR related neurotoxicity is lacking. The results of this study may contribute to early diagnostics of vincristine based neurotoxicity, and identification of patients especially at risk regarding neurotoxic effects.

Atorvastatin lactonization is associated with statin-dependent muscular side effects in patients with coronary heart disease

Md, Phd Candidate Trine Lauritzen[1,2], Professor John Munkhaugen[1,2], PhD Kari Peersen[4], PhD Oscar Kristiansen[1], PhD Elise Sverre[3], Anders M Andersen[3], Professor Stein Bergan[3,4], MD, PhD Einar Huseby[1], PhD Nils Tore Vethe[3]
[1]Vestre Viken Hospital Trust, Drammen, Norway, [2]University of Oslo, Oslo, Norway, [3]Oslo University Hospital, , Norway, [4]Vestfold Hospital Trust, , Norway

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction
Statin-associated muscle symptoms (SAMS) is a prevalent cause of statin discontinuation, leading to unfavorable clinical outcome. In clinical practice, it is challenging and time-consuming to assess whether self-perceived SAMS are caused by the statin or not, and diagnostic biomarkers are therefore requested. Atorvastatin (ATV) metabolites, especially the lactones, have been associated with statin-dependent muscular side effects. We aimed to assess atorvastatin metabolites as potential diagnostic biomarkers for statin-dependent muscular side effects in skeletal muscle tissue and blood plasma as potential diagnostic biomarkers for statin-dependent muscular side effects among patients with coronary heart disease (CHD).
Materials and Methods
In 2020, a biomarker follow-up study included 26 CHD patients with self-perceived SAMS who had participated in a previous randomized double-blinded crossover trial (ATV 40 mg/day and matched placebo) as well as a statin tolerance follow-up study. In the biomarker study, all participants received open treatment with ATV 40 mg/day for seven weeks followed by no statins for eight weeks. Muscle biopsies were collected from the vastus lateralis of the quadriceps muscle after the ATV treatment period (n=26) and after the no-statin period (n=23), and they underwent histological examination. Blood was collected both pre-dose at the time of biopsy (T0) and one and two hours after statin intake (T1 and T2). ATV and its major metabolites were measured in muscle and blood plasma with liquid chromatography tandem mass spectrometry. Mann-Whitney test and ROC-analyses were performed with SPSS.
Results
A subgroup of four patients had histological signs of statin-dependent necrotic muscle fibres and four patients did not tolerate any statins (n=2) or only pravastatin or simvastatin 20 mg/day (n=2). One patient was in both groups. These seven patients were categorized as having statin-dependent muscular side effects.
In muscle tissue, the sum of acid metabolites and the sum of lactone metabolites were significant lower in the clinically statin-intolerant patients ($p=0.003$ and $p=0.042$), and the ratio between the sum of lactones and acids in muscle was elevated (5.2 vs. 2.5, $p=0.012$). A corresponding pattern was observed in blood plasma from the same patients ($p<0.05$). The lactone/acid ratio tended to be higher in patients present with necrotic muscle fibers on ATV (not statistically significant). A ROC curve analysis of the ratio between sum of lactones and acids (pooled intolerant and/or necrotic muscle fibers vs. no muscular side effects) provided 100% sensitivity and 53% specificity for muscle tissue measurements (cut-off 2.6), and 86% sensitivity and 68% specificity for plasma measurements (T1, cut-off 0.9).
Discussions and Conclusions
Our results indicate that the pharmacokinetics of atorvastatin is skewed towards increased lactonization in statin-intolerant patients. Atorvastatin lactone/acid ratios measured in blood plasma appear as promising biomarkers for statin-dependent muscular side effects. The clinical relevance of necrotic muscle fibers in relation to statin treatment has yet to be clarified. Our study provides candidate cut-off values that should be pursued further for the determination of diagnostic sensitivity and specificity.

The role of pharmacogenetics as a possible risk factor for dabigatran–associated bleeding

Jozefina Palić[1], Assistant professor Lana Ganoci[2], PhD Livija Šimičević[2], Assistant professor, MD Majda Vrkić Kirhmajer[3], MD Hrvoje Holik[4], Student Ivana Prpić[5], Assistant professor Tamara Božina[1]
[1]Department of Medical Chemistry, Biochemistry and Clinical Chemistry, University of Zagreb, School of Medicine, Zagreb, Croatia, [2]Division of Pharmacogenomics and Therapy Individualization, Department of Laboratory Diagnostics, University Hospital Centre Zagreb, Zagreb, Croatia, [3]Department of Cardiology, University Hospital Centre Zagreb, University of Zagreb, School of Medicine, Zagreb, Croatia, [4]Department of Internal Medicine, "Dr. Josip Benčević" General Hospital, Slavonski Brod, Croatia, [5]Faculty of Pharmacy and Medical Biochemistry, University of Zagreb, Zagreb, Croatia

Poster session 2 - Tuesday, september 26, 2023, 13:00 - 14:30

INTRODUCTION

Dabigatran is a direct oral anticoagulant (DOAC) administered as prodrug dabigatran etexilate. Dabigatran etexilate is a substrate of intestinal efflux transporter ABCB1 (P-glycoprotein) and after absorption, it is transformed mainly by liver carboxylesterase (CES1) to an active metabolite. Dabigatran has substantial interindividual pharmacokinetic variability associated with age, sex, renal function, concomitant illness and therapy, which affects its efficacy and safety. Clinically relevant drug-drug interactions (DDIs) of dabigatran are mainly related to the concomitant use of P-glycoprotein substrates or inhibitors. Genetic variability of CES1 and ABCB1 genes can affect the pharmacokinetics of dabigatran and potentially the risk of bleeding. The aim of our study is to investigate the role of pharmacogenetics as a possible risk factor for dabigatran bleeding and thromboembolic events in cardiovascular diseases.

PATIENTS AND METHODS

The presented results are preliminary data of the larger cohort "Pharmacogenomics in Prediction of Cardiovascular Drugs Adverse Reaction (PGx-CardioDrug)". Clinical and laboratory data were collected (dabigatran doses, diagnosis, comorbidities, GFR, creatinine level) with bleeding and thromboembolic events as outcomes. Genotyping of CES1 c.257+885T>C (rs8192935) and ABCB1 c.1236C>T (rs1128503), c.2482-2236G>A (rs4148738), c.2677G>T/A (rs2032582) and c.3435C>T (rs1045642) variants was performed by real-time PCR with specific TaqMan® SNP and DME Assays on ABI 7500 Real-Time PCR System and in-house method on LightCycler. Associations between carriers and noncarriers of variant alleles or haplotypes and bleeding events were analysed. Drug-drug interactions were evaluated with Lexicomp® Clinical Decision Support System. Statistical analysis was performed by JASP 0.17.1 software.

RESULTS

Of 1027 patients from the study cohort, 422 patients were treated with DOAC-s and among them 80 patients with dabigatran etexilate (median age 70, range 21-93, female=35, male=45), mainly from a tertiary care setting. For all analysed variants, genotype distribution was consistent with Hardy Weinberg's equilibrium. Number of patients per variant were (non-carriers/heterozygotes/homozygotes): CES1 c.257+885T>C (7/39/34), ABCB1 c.1236C>T (28/34/18), c.2482-2236G>A (27/36/17), c.2677G>T/A (31/30/19) and c.3435C>T (21/32/27). Twenty-six patients had dabigatran-associated bleeding (median age 77 years, range 43-93, female=17, male=9): anaemia (N=13), gastrointestinal (N=11), epistaxis (N=3), haematoma (N=5), overdosing (N=7), gingival (N=1) and gynaecological bleeding (N=1). Among patients with bleeding events, at least one bleeding risk factor was observed (age, impaired renal function, DDIs, genetics). Fifteen patients were exposed to at least one (1-6) dabigatran DDI of C, D or X level of severity with a potentially higher risk of bleeding, ten patients had impaired renal function; variant distribution is CES1 c.257+885T>C (3/14/9), ABCB1 c.1236C>T (10/9/7), c.2482-2236G>A (10/10/6), c.2677G>T/A (11/9/6) and c.3435C>T (6/12/8). Only six patients had a thromboembolic event and were not included in the analysis. We found no significant association between CES1 c.257+885C, ABCB1 variant alleles or

1236T-2677T/A-3435T haplotype nor cumulative CES1 c.257+885C, ABCB1 variant or 1236T-2677T/A-3435T haplotype with risk of bleeding.

DISCUSSIONS AND CONCLUSIONS

There is no significant association between CES1(rs8192935) or ABCB1 variants with dabigatran-associated bleeding, which is expected because of the sample size. Our data suggest a possible role of pharmacogenetics in interaction with other clinical factors in predicting dabigatran-associated bleeding and indicate the need for further comprehensive research on a larger sample.

Distinguishing multimer from dimer antidrug antibody complexes with infliximab or adalimumab using HMSA is relevant to drug dosing decisions

Ms Paula Keating[1], Dr John O'Donnell[1], Professor Murray Barclay[2]
[1]Canterbury Health Laboratory, Te Whatu Ora-Health New Zealand, Christchurch, New Zealand,
[2]Christchurch Hospital, Te Whatu Ora-Health New Zealand, Christchurch, New Zealand

Biologicals, Sal B, september 26, 2023, 13:00 - 14:30

Development of antidrug antibodies (ADA) to infliximab or adalimumab often means that the drug needs to be exchanged for another treatment. This judgement is often based on the antidrug antibody titre, i.e. high versus low. Antibody titre definitions can vary widely between laboratories. However, our data suggest that the size of the drug/antibody complex may be more important than the titre. ADA may be neutralising, binding to the antigen binding sites leading to loss of drug function and need to change the drug, or non-neutralising enhancing drug clearance, which can be overcome with dose increase. A feature of the HMSA method is that the size of in vitro formed drug-ADA complexes is measured, distinguishing multimeric from dimeric ADA-drug complexes in samples. In a review of our laboratory test service we found that 48% of samples (612/1263) with drug concentration <2mg/L were ADA positive. Over 80% (489/612) of ADA positive samples formed dimer complexes of drug and ADA in vitro. The dimer complexes were not associated with complete drug neutralisation. Conversely, it was the samples with multimeric immune complexes, that also contained IgG4 isotype ADA, that neutralised drug action. Determination of size of immune complex formed by ADA and drug in vitro will be useful in determining drug dosing decisions and may be more important than antidrug antibody titre.

Cefotaxime dosing strategy and target concentrations should be reconsidered in critically-ill patients

Théo Dillie[1], Pr Guillaume Thiery[1], Pr Jérôme Morel[1], Dr Rémi Balluet[1], Dr Manon Launay[1], Dr Sophie Perinel-Ragey[1]
[1]Chu Saint Etienne, Saint Etienne, France

Anti-infectives 1 - antibiotics and antifungals, Sal B, september 25, 2023, 13:00 - 14:30

According to its Summary of Product Characteristics, cefotaxime should be administered using 3-12g/day depending on the severity of the infection, in all adults with creatinine clearance (CrCl) higher than 5ml/min. For undocumented infections, theoretical threshold range is 25-60mg/L. As 80% of cefotaxime intravenous dose is excreted in urine, the aim of this study was to investigate the impact of change in renal function on cefotaxime concentrations and subsequent clinical impact.

This retrospective cohort study was conducted at Saint Etienne University Hospital (France) between December, 2020 and March, 2022. The study was approved by the Institutional Review Board [IRBN992021/CHUSTE]. All consecutive critically ill patients with cefotaxime continuous infusion monitored at steady state were included in this study. Doses were not constant during the study, with variable exposure but linear pharmacokinetics, justifying consideration of the concentration-versus-dose ratio (C0/D). Clinical improvement was defined as a decrease in SOFA score higher than or equal to 2 between the time of last cefotaxime measurement and treatment introduction.

A total 73 patients (51 males, 35 obeses), aged 58±14 years, were included. The most common site of bacterial infection was pulmonary (50/73) and 27 patients (37 %) had COVID infection. The average length of stay in ICU was 24±20 days. Average SOFA score was 8.2±3.7 before cefotaxime introduction. Seventeen patients (23,3 %) died before leaving intensive care unit. Clinical improvement was observed in 9/58 patients with available data and average glomerular filtration rate and weight were identified as significant covariates with odds ratio of 0.96 [0.93 – 0.99] and 0.92 [0.85 – 0.97], respectively. However, mean cefotaxime concentrations were significantly different according to CrCl (ANOVA test, $p<0.0001$*), with 68±32 mg/L for CrCl between 5 and 30 ml/min, to 27±16 mg/L for CrCl above 130 ml/min, despite similar dosing. Cefotaxime concentrations were therefore significantly different between improved and not improved patients (54.4 versus 35.0 mg/L, $p=0.01052$*, t-test). According to a Receiver Operating Characteristic curve, average cefotaxime concentration among treatment higher than 51 mg/L was associated with a clinical improvement with a specificity of 86% and a sensitivity of 67%. Average C0/D were respectively 3.5, 6 and 11 in patients with respectively severe renal impairment (i.e CrCl between 5-30 ml/min, observed in 12% of the patients), normal renal function and augmented renal clearance (ARC, i.e CrCl above 130 ml/min, observed in 15% of the patients).

These results suggested that concentration higher than 50 mg/L was associated with clinical improvement in ICU patients, rather than the theoretical threshold of 25 mg/L based on calculation upon free fraction higher than 4 times the MIC. Because patients were mostly sedated, no further investigation has been performed on the toxicity threshold. Furthermore, CrCl was significantly associated with cefotaxime exposure, including in ARC patients, which is supported by recent studies showing that GFR is a significant covariate influencing cefotaxime clearance. Cefotaxime dosing strategy should be reconsidered with (3.5/6) 50% decreased amount in severe renal impaired patients and (11/6) 50% increased amount in ARC patients. Prospective clinical studies are mandatory to confirm these results.

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The association between reached therapeutic range of valproic acid and seizure control in Thai pediatric epilepsy patients

Dr. Suthida Boonsom[1,2], Chutikan Sriprom[1], Phatcharin Sinthao[1], Pennipa Sukhpimai[1]
[1]Department of Pharmaceutical Care, School of Pharmaceutical Sciences, University of Phayao, Muang, Thailand, [2]Unit of Excellence on Pharmacogenomic Pharmacokinetic and Pharmacotherapeutic Research (UPPER), School of Pharmaceutical Sciences, University of Phayao, Muang, Thailand

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Background: The therapeutic range of valproic acid is 50-100 mcg/mL, which has been shown in many studies to control seizures. Whereas some studies indicate that patients can control their seizures even at doses below the therapeutic range.
Objective: This study aimed to determine the association between reached therapeutic range of valproic acid and seizure control in Thai pediatric epilepsy patients.
Methods: The study was a retrospective cohort study. Data were collected from electronic medical records at Chiangrai Prachanukroh Hospital between 1 January 2015 and 31 December 2021. Patients under 18 years diagnosed with epilepsy who had been monitored for valproic acid concentration were included in this study. The factors studied included sex, age, body weight, serum concentration, co-medications, co-morbidity, valproic acid daily dose, compliance, dosage form, serum albumin, serum creatinine, and renal function. To find a relationship between factors and seizure control (control/uncontrol), data were analyzed by logistic regression (univariate and multivariate analysis) with p-values < 0.05.
Results: A total of 57 Thai pediatric epilepsy patients met the study criteria. The average age was 87.95±62.35 months, mostly 35 males (61.40%), and 22 females (38.60%). The average weight was 24.03±15.19 kg. The average daily dose was 648.36 mg. The average serum valproic acid concentration was 55.19±32.13 mcg/mL. Twenty-one (36.84%) patients whose blood levels were below the therapeutic range, thirty patients (52.63%) were in the therapeutic range and six patients (10.53%) were above the therapeutic range. Thirty-five patients (61.40%) received co-medications for anti-epilepsy drugs and twenty-two patients (38.60%) received valproic acid alone. The relationship between reached therapeutic range of valproic acid and seizure control did not show statistical significance (P-values=0.507). Every one percent increase in reaching the therapeutic range was not associated with a 0.996 reduction in the odds of seizure control (95% CI 0.983 to 1.008). However, the factor associated with seizure control was the average daily dose (OR 0.99 [95% CI 0.996 to 0.999]; P-values=0.022).
Conclusions: There is no significant association between the reached therapeutic range of valproic acid and seizure control. However, this study found that the factors associated with seizure control in Thai pediatric epilepsy patients were the average daily dose which can be concluded that an increased average daily valproic acid dose was associated with reduced seizure control.

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Detection and quantitation of protonitazene in a case of acute respiratory arrest

Mr Jon Andsnes Berg[1], Mr Marcus Stangeland[1], Mr Torbjørn Lunde[1], Mr Kjell Ove Fossan[1]
[1]Haukeland University Hospital, , Norway

Poster session 1 - Monday, september 25, 2023, 13:00 - 14:30

Introduction

Protonitazene is a highly potent synthetic opioid, that was first synthesized in the 1950s, but was never implemented because of the risk of adverse effects. It was first detected in human samples in 2021. We report the first detection and quantitation in serum and urine in Norway in a patient with respiratory arrest. The patient responded transiently to 0,4 mg and required altogether 2,0 mg before regaining consciousness. The patient admitted taking a nasal spray, being told it contained an opioid.

Materials and Methods

A serum and a urine sample were obtained at admission and after 7 hours, respectively. The initial screening was performed in the urine sample with cloned enzyme donor immunoassay (CEDIA, Thermo Fisher Scientific) for commonly used drugs of abuse on the Beckman AU680. Further analyses were performed using a Sciex X500r LC-QTOF-MS with a routine repertoire of 43 substances and metabolites as previously published, including several opioids, and an extended calibrator, consisting of 126 substances, including several synthetic opioids. The urine sample was analyzed diluted 10 times with and without treatment with β-glucuronidase. Protein precipitation and dilution was used for the serum sample. A targeted search for benzimidazole opioids (nitazenes) was performed based on published data, as the spectral libraries did not contain any of these compounds. Quantitative analysis of protonitazene was performed using a Sciex Citrine LC-MS/MS.

Results

The initial screening of a urine sample with immunoassay showed negative results. Only naloxone was detected with the LC-QTOF-MS method. Because of a strong suspicion of opioid intoxication, a non-targeted screening was performed, with a pattern that could match isotonitazene. After acquiring reference material, the presence of protonitazene in the urine sample was confirmed. Quantitative analysis showed a serum concentration of 0,65 ng/mL and a concentration of 0,13 ng/mL in urine.

Discussions and Conclusions

There is a lack of data on concentrations in non-fatal intoxications with protonitazene. The serum concentration of protonitazene in the present case is lower than previously described in post-mortem cases (1,3-1400 ng/mL). The patient was opioid naïve, and therefore probably non-tolerant. Some of the metabolites of protonitazene are as potent as the parent substance. These factors might have contributed to the serious intoxication despite the presumable low serum concentration.

Impact of age and sex on the exposure of six antipsychotics, based on routine therapeutic drug monitoring (TDM) data from 20 000 patients

Vigdis Solhaug

Psychiatry, Møterom 4, september 25, 2023, 13:00 - 14:30

Introduction
Elderly patients are more prone to adverse effects of antipsychotics. One reason may be that they are exposed to higher serum concentration, given the same dose, compared to young persons. As clinical drug trials often exclude the old population, the aim of this study was to use real world TDM data to investigate the impact of age and sex on the exposure of six commonly used antipsychotic drugs.

Method
The study was based on TDM data collected at the Center for Psychopharmacology, Diakonhjemmet hospital (Oslo, Norway) from the period January 2010 to November 2022. Serum concentration samples from patients above 18 years, using therapeutic doses of amisulpride, aripiprazole, clozapine, olanzapine, risperidone and zuclopenthixol were included. Sample information was extracted from the requisition forms including information about age, gender and daily dose. The included serum concentration measurements were sampled 10-26 hours after the last dose intake. As a measure of exposure, daily dose-adjusted serum concentration (C:D ratio) of the six antipsychotics was used. Samples were grouped in three age groups: 18-49 years, 50-74 years or ≥75 years. Linear mixed model analysis were used to allow for inclusion of multiple samples per patient.

Results
For the different antipsychotics, the following number of samples (patients) were included: Amisulpride: 1 944 (559), aripiprazole: 9 555 (3 679), clozapine: 27 096 (2 258), olanzapine: 23 716 (8 770), risperidone: 9 282 (3 806) and zuclopenthixol; 2 768 (896). Mean age for patients using the six antipsychotics range from 42.8 years (aripiprazole) to 52.5 years (zuclopenthixol). Compared to young males (18-49 years), males above 75 years had higher estimated mean exposure of these antipsychotics (aripiprazole: +5.9%, $p=0.392$, zuclopenthixol: +12.7%, $p=0.253$, olanzapine: +34.5%, $p<0.001$, clozapine: +46.1%, $p<0.001$ and risperidone: +80.6%, $p<0.001$, amisulpride: to few samples). For the elderly females above 75 years the mean exposure was even higher and significant for all six antipsychotics, compared to males 18-49 years (zuclopenthixol: + 37.3%, $p<0.001$, aripiprazole: +41.0%, $p<0.001$, clozapine: +48.1%, $p<0.001$, olanzapine: +68.9%, $p<0.001$, amisulpride: +84.0%, $p<0.001$, risperidone: +121.7%, $p<0.001$).

Conclusions
Both male and female patients above 75 years were exposed to significantly higher levels of most antipsychotics, compared to males under 50 years. The increase in exposure ranged from a 5.9% increase for aripiprazole in men above 75 years to 121.7% increase for risperidone in the oldest females. The antipsychotic exposure was higher in females than in males, leaving the oldest females with higher risk of dose dependent adverse effects.

Ultrarapid metabolism of non-clozapine antipsychotics preceding switch to clozapine treatment

Hasan Çağın Lenk[1,2], Robert Løvsletten Smith[1], Espen Molden[1,2]
[1]Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway, [2]Section for Pharmacology and Pharmaceutical Biosciences, Department of Pharmacy, University of Oslo, Oslo, Norway

Psychiatry, Møterom 4, september 25, 2023, 13:00 - 14:30

Introduction: Clozapine is superior to other antipsychotics in treatment of schizophrenia. However, due to the risk of severe side-effects, clozapine is only indicated for use in patients with treatment-resistant schizophrenia (TRS). Although, adequate exposure to non-clozapine antipsychotic treatment is a requirement before switching to clozapine, we have previously showed that many patients do not fulfil this criterion. In this study, we aimed to describe the frequency of TRS patients exhibiting low concentration phenotypes of non-clozapine antipsychotics and their respective metabolizer status preceding clozapine treatment.
Materials and Methods: The study population consisted of 663 patients with a therapeutic drug monitoring (TDM) history of non-clozapine antipsychotics (aripiprazole, risperidone, olanzapine, or quetiapine) within one-year preceding clozapine treatment. Patients were included from the TDM service at Center for Psychopharmacology in Oslo, Norway. To define serum concentration phenotypes, a threshold dose-adjusted concentration (CD) was calculated from all existing TDM registries of each orally administered antipsychotics. Patients were defined as 'low concentration phenotype' (cases) if they had at least one antipsychotic measurement with a CD below the threshold CD, i.e. below the 25% percentile. Patients with CD measurements higher than the threshold served as controls. Metabolic ratios of antipsychotics were then compared between patients with low concentration phenotypes and the controls.
Results: 30% of the study population (n = 201) exhibited low concentration phenotypes before switching to clozapine. Compared to controls, patients with low concentration phenotypes were prescribed significantly higher total daily doses of aripiprazole (1.29-fold; $p = 0.006$), olanzapine (1.14-fold; $p = 0.018$), quetiapine (1.62-fold; $p = 0.001$), and risperidone (1.30-fold; $p = 0.005$). Furthermore, low concentration phenotypes were associated with significantly increased metabolic ratios for aripiprazole (fold-change: 1.27; $p = 0.003$), olanzapine (fold-change: 1.59; $p < 0.0001$), quetiapine (fold-change: 3.08; $p < 0.0001$), and risperidone (fold-change: 4.50; $p < 0.0001$) measurements compared to controls.
Conclusion: The study shows that low concentration phenotypes of non-clozapine antipsychotics are frequent before switching to clozapine and for many patients associated with unexplained, ultrarapid metabolism.

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