**Population pharmacokinetics of penicillin G: insights into in-creased clearance at low concentrations to guide development of improved long-acting formulations for syphilis and prevention of rheumatic fever**

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**Background and aims.** While benzylpenicillin (penicillin G) is listed by the WHO as an Essential Medicine, dose optimisation is a persistent challenge, especially for long-acting IM formulations. Maintaining sustained antibiotic exposure at target concentrations is crucial for secondary chemoprophylaxis of rheumatic heart disease and treatment of syphilis. This study compared the pharmacokinetic profile of continuous low-dose benzylpenicillin infusions with a standard-dose bolus, and evaluated which renal function marker (serum creatinine, cystatin C, or combined eGFR) best predicted clearance.

**Methods.** Healthy adult volunteers received a single 600 mg IV benzylpenicillin bolus followed by randomisation to continuous infusions targeting steady-state concentrations of 3, 6, 9, 12, or 20 ng/mL1. Plasma benzylpenicillin concentrations were measured by liquid chromatography–mass spectrometry2. Population pharmacokinetic analysis was performed using NONMEM by incorporating both bolus and infusion data, while various GFR estimations were evaluated as covariates for clearance.

**Results.** Data from 72 participants were analysed, including 504 bolus and 389 continuous infusion samples. A two-compartment model improved fit when the ratio of central volume of distribution between bolus and low-dose infusion was incorporated, and clearance differences at steady state plasma concentration of 3 ng/mL were accounted for. Of the GFR estimations, cystatin C–based eGFR significantly enhanced model fit compared to creatinine-based equations.

**Conclusion/Discussion.** Benzylpenicillin pharmacokinetics at very low concentrations demonstrated both a higher volume of distribution and increased clearance. Cystatin C–based eGFR may more accurately predict benzylpenicillin clearance, enabling precision dosing for long-acting preparations used for treatment of syphilis and prevention of rheumatic fever.

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**References:**

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