**Understanding the pharmacokinetics of enteric coated sodium valproate in overdose**

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**Introduction:** A challenge to establishing best practice in response to overdose involving sodium valproate (VPA) is the limited pharmacokinetic data at doses well above the therapeutic range. This impacts the ability to accurately predict clinical course, initiate early interventions to prevent neurological sequalae before reaching toxic concentrations, and to measure the effectiveness of new interventions. One such treatment of interest is administration of meropenem, which has the potential to rapidly increase VPA elimination and attenuate toxicity in overdose. The parameters of clinical relevance are maximum plasma concentration (Cmax), time to peak plasma concentration (tmax) and half-life (t1/2).

**Aims:** To build and verify a physiologically based pharmacokinetic model describing the kinetics of exposure to enteric coated (EC) sodium valproate (EC-VPA) in overdose, and the effect of administering meropenem.

**Methods:** A minimal PBPK model for EC-VPA was built and verified using the Simcyp Simulator (version 19.1). The model incorporated an advanced dissolution, absorption and metabolism (ADAM) absorption model with a monolithic system solid modified release formulation and concentration dependent plasma protein binding profile. EC-VPA elimination was defined based on enzyme kinetics as the Km and Vmax for individual metabolic pathways to enable assessment of saturable clearance pathways. The performance of the model was verified by comparison to published plasma concentration time profiles for EC-VPA. The impact of meropenem administration on EC-VPA exposure was simulated by adjusting the percentage of EC-VPA available for reabsorption and scaling Vmax for UGT medicated elimination pathways. Virtual clinical trials were performed in n=120 healthy subjects aged 18 to 50 years (50% female).

**Results:** At a 500 mg dose the kinetics of simulated EC-VPA exposure reflected the concentration time profile observed in clinical trials; tmax , Cmax, AUC and t1/2 were 4.5 hrs, 45.2 mg/L, 1,115 mg/L.hr, and 16.1 hrs, respectively. Prolonged tmax and t1/2 , and non-dose proportional increase in Cmax were observed in overdose. Co-administration of meropenem resulted in only minor attenuation of Cmax, but a 2-fold reduction in t1/2, consistent with increased clearance.

**Discussion:** A PBPK model describing the kinetics of EC-VPA exposure at doses up to 110 g was built and verified. This model may be applied to interrogate the effectiveness of various interventions to minimise VPA exposure in overdose including administration of activated charcoal and administration of meropenem.