Physiologically Based Pharmacokinetic (PBPK) Modeling of Meropenem Pharmacokinetics in Healthy and Renally Impaired Adults

Andrew Castleman and Joel S Owen

Union University School of Pharmacy, Jackson, TN

Objectives: Develop a PBPK model for intravenous meropenem administered to healthy adults and adults with impaired renal function validated by reported data from literature. Further development is planned to incorporate dialysis as an additional route of elimination.

Methods: Meropenem’s pharmacokinetics were simulated using the PBPKPlus™ Module of GastroPlus™ 9.0, and data were collected from published tables and graphs using GetData Graph Digitizer 2.24. The Population Estimates for Age-Related (PEAR) Physiology™ module was used to generate physiologies matching the average demographics (gender, weight and age) of the subjects from which data were obtained. Physiological and physiochemical parameters were predicted by GastroPlus™ or obtained from literature. No parameters were optimized. Total clearance consists of renal and non-renal mechanisms. Clearance values were estimated by equations derived from linear regression relating renal (CLR: mL/min) and total clearance (CL: mL/min) of meropenem to subjects’ creatinine clearances (CrCl: mL/min). The difference of the renal and total clearance was assumed to be hepatic clearance.

Results: A single PBPK model was able to accurately predict the plasma concentrations of healthy adults (250-1000mg) and renally impaired adults (500mg) after intravenous meropenem administration. All predicted AUCs were within a 2-fold range of literature reported AUC values as shown in Table 1. Linear regression resulted in the equations used for clearance: CLR=1.877xCrCl-6.792 (R^2=0.95) and CL=2.255xCrCl+25.7 (R^2=0.89).

Conclusions: Using linear equations to define the clearance terms of the PBPK model resulted in accurate predictions of meropenem pharmacokinetics in healthy and renally impaired adults. This model is suitable for further development to explore dialysis as an elimination pathway.

References: