Physiologically Based Pharmacokinetic (PBPK) Model for Prediction of Vancomycin Pharmacokinetics in Children

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Purpose
Ethical considerations prevent extensive clinical trials in pediatric populations; however, with the use of PBPK modeling, in vivo data from adults can be used to explore the mechanisms of drug disposition and pharmacokinetics (PK) in children following a variety of administration routes. Simulation tools allow exploring the sensitivity of exposure to individual processes involved in drug absorption, distribution, and elimination, and so can help in design of the trials to maximize their efficiency. Several studies were published in the past demonstrating the accuracy of PBPK models in predicting pediatric PK for compounds with simple (perfusion-limited) tissue distribution and elimination mainly by CYP metabolism. For this study, vancomycin was selected for its very low membrane permeation that is not captured well by perfusion-limited tissue models, and for its elimination by renal secretion. Rapid changes in glomerular filtration rate (GFR) in the first few weeks after birth and the effect of both gestational age (GA) and postnatal age (PNA) add to the variability in clearance in neonates. Changes in body water content and distribution also affect drug distribution throughout the body and need to be accounted for when trying to predict PK for this age group.

Methods
Vancomycin pharmacokinetics was simulated using the PBPKPlus™ module in GastroPlus™ 9.0 (Simulations Plus, Inc., Lancaster, CA). To account for the low diffusion of vancomycin through cell membranes, all tissues were treated as permeability-limited tissues. Organ weights, volumes, and blood perfusion rates were generated by the program’s internal Population Estimates for Age-Related (PEAR™) Physiology module. Renal clearance was estimated from GFR and fraction unbound in plasma (Fup*GFR). Tissue/plasma partition coefficients (Kp’s) were calculated using Poulin’s equation for drug partitioning into extracellular space (Poulin 2002) from in vitro and in silico physicochemical properties (ADMET Predictor™ 7.2, Simulations Plus, Lancaster, CA). The permeability-surface area products (PStcs) for individual tissues were calculated as the product of the Specific PStc (PStc per mL of tissue cell volume) and total cell volume of each tissue. The single value of Specific PStc used for all tissues was fitted against in vivo plasma concentration-time (Cp-time) data after i.v. administration of vancomycin in rats. The model was subsequently used to predict the vancomycin PK in human adults and to explore the sources of variability in vancomycin PK. Finally, the model was refined using the adult data. Vancomycin PK in different pediatric groups, including neonates and infants, was then predicted. The importance of GA vs PNA on vancomycin PK was explored.

Results
The PBPK model developed using PK data in rats resulted in excellent prediction of vancomycin PK in adult humans. The model refined from adult data was successfully scaled to predict PK in children, including neonates and infants. By accounting for effect of both GA and PNA on the ontogeny of GFR, and changes in body water, the model using built-in neonatal physiologies was also able to predict the variability in vancomycin PK in this age group.

Conclusion
This study demonstrates the utility of PBPK modeling throughout the drug development continuum, starting with modeling in preclinical species, followed by first-in-human prediction, and finally predicting PK in pediatric groups. PBPK methodology also offers the opportunity to isolate contributions of individual physiological processes, to explore the sources of variability in PK, and to highlight the physiological parameters to consider when deciding the starting dose for individual patients. The presented example also shows the application of predicting pediatric PK for a compound where the distribution is not well-predicted by standard methods for tissue/plasma partition coefficients and requires characterization of the kinetics of diffusion through the cell membranes.