Physiologically based pharmacokinetic (PBPK) model for prediction of vancomycin pharmacokinetics in children

Lukacova, V., W.S. Woltosz, M.B. Bolger

Simulations Plus, Inc. Lancaster, California, USA; correspondence should be addressed to: viera@simulations-plus.com

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 physiologic processes to PK, including neonate physiology, to provide insight into the distribution of vancomycin in vivo. To highlight the physiologic parameters to consider when deciding the starting dose for individual patients. The presented example also shows the application of predicting pediatric PK 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.

The PBPK model was calibrated by fitting Specific Psic (fitted value 2.5e-5 mL/s/mL cell volume) against the observed Cpit profile after 5mg/kg i.v. administration of VCN in rats, and verified by predicting VCN plasma and kidney concentrations in rats after 100 mg/kg i.v. administration (Figure 1). The model developed using PK data in rats resulted in excellent prediction of VCN PK in adult humans (Figure 2). Finally, the model was successfully scaled to simulate PK in infants. By accounting for the effects of both GA and PNA on the ontogeny of GFR, and changes in body water, the model used building neonatal physiologies was also able to predict the variability in VCN PK in this age group.

Sensitivity analysis was performed to explore the effect of rapid physiologic changes in the first few weeks after birth as well as the effect of GA and PNA on the PK of VCN in neonates and infants. Different physiologies for infants with GA 25 to 40 weeks and PNA 2 days to 20 weeks were generated using inbuilt algorithms in GastroPlus 9.0. VCN PK after 15 mg/kg i.v. dose was simulated for each virtual infant and clearance was calculated from dose and simulated AUC. The CL was compared to the variability in CL from a Population PK (PopPK) model fitted to data from an infant clinical study [6]. The PBPK model resulted in excellent prediction of VCN CL in this age group (Figure 4) by considering the influence of both GA and PNA on ontogeny of GFR (Figure 5).

References

1. Shimada – Antiretroviral Pharmacology 2012, 32: 823-829
7. GastroPlus manual, version 9.0 (Simulations Plus, Inc.)