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

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Aim

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 (VCN) 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

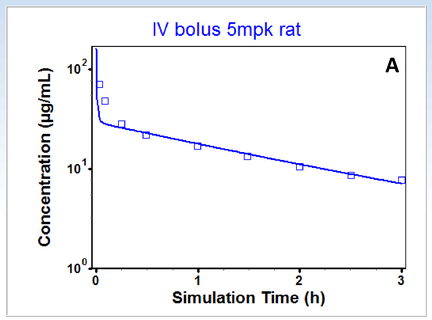
VCN pharmacokinetics was simulated using the PBPKPlus™ module in GastroPlus™ 9.0 (Simulations Plus, Inc., Lancaster, CA). To account for the low diffusion of VCN through cell membranes, all tissues were treated as permeability-limited tissues. Organ weights, volumes, and blood perfusion rates were generated 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 VCN in rats. The model was subsequently used to predict the VCN PK in human adults. After validating against adult data, the model was used to predict VCN PK in different pediatric groups, including neonates and infants. The importance of GA vs PNA on VCN PK was explored.

Conclusions

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.

Results

The PBPK model was calibrated by fitting Specific PStc (fitted value 2.5e-5 mL/s/mL cell volume) against the observed Cp-time 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 predict PK in children, including neonates and infants. By accounting for the effects 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 VCN PK in this age group.



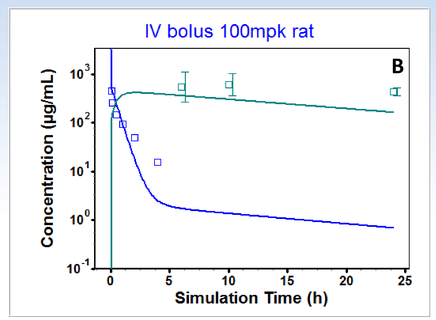
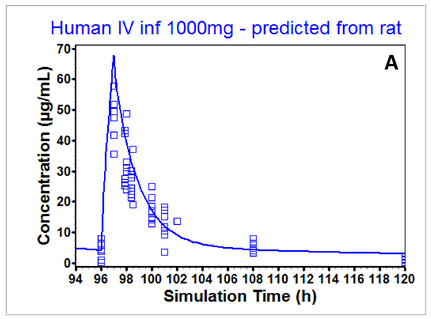


Figure 1: Simulated (lines) and observed (points) VCN plasma (blue) and kidney (dark cyan) concentration time profiles in rat after i.v. administration 5 mg/kg (A) and100 mg/kg dose (B). The Cp-time profile after 5mg/kg dose was used to calibrate the model (fit Specific PStc value). Both plasma and kidney concentration-time profiles after 100 mg/kg dose were predicted using the Specific PStc fitted against only the plasma data for 5 mg/kg dose. Experimental data were obtained from [1-2]. Simulations were performed using default rat physiologies in GastroPlus 9.0, experimental Fup and GFR as reported in each study, and an *in silico* (ADMET Predictor v7.2) value for blood/plasma concentration ratio (Rbp = 0.68)



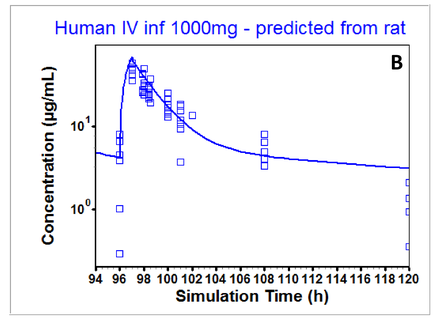
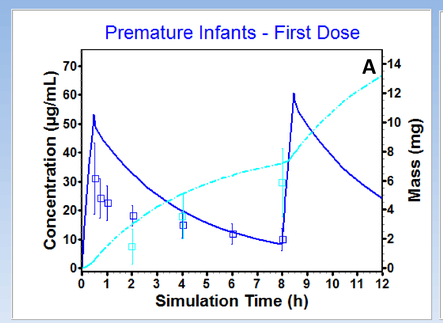


Figure 2: Simulated (lines) and observed (points) VCN steady-state Cp-time profile after i.v. administration of 1000 mg dose in healthy adult volunteers shown on linear scale (A) and log scale (B). Experimental data were obtained from [3]. Simulations were performed using default physiology and GFR in GastroPlus 9.0 for adult human matching age and weight of subjects from the reported study (24-years-old, 84.3kg), experimental Fup [4], *in silico* (ADMET Predictor v7.2) value for Rbp, and Specific PStc as fitted against observed VCN Cp-time profile in rats.

References

[1] Shimada – Anticancer Res 2012, 32: 823-829
[2] Kusama – J Pharm Sci 1998, 87: 1173-1176
[3] Lodise – Antimicrob Agents Chemother 2011, 55: 5507-5511
[4] Butterfield – Antimicrob Agents Chemother 2011, 55: 4277-4282
[5] Reed – Ped Res 1987, 22: 360-363
[6] Grimsley – Arch Dis Child Fetal Neonatal Ed. 1999, 81: F221-F227
[7] GastroPlus manual, version 9.0 (Simulations Plus, Inc.)



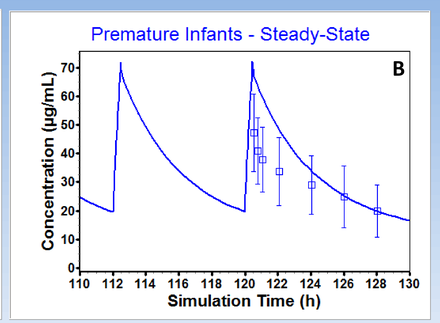


Figure 3: Predicted (lines) and observed (points) VCN Cp-time profile (blue) and cumulative amount excreted in urine (cyan) in premature infant (20-days-old, born 12 weeks premature, body weight 1.07kg) after i.v. administration of 12.6 mg/kg dose after first dose (A) and in steady-state (B). Experimental data were obtained from [5]. Simulations were performed using default physiology and GFR in GastroPlus 9.0 for premature infant matching GA, PNA, and weight of subjects from the reported study, Fup and Rbp scaled from adult values using the built-in scaling function in GastroPlus 9.0 based on age-dependent changes in plasma albumin levels and hematocrit, and Specific PStc calibrated using rat data (Figure 1), and validated by simulation of adult human PK (Figure 2).

Sensitivity analysis was performed to explore the effect of rapid physiological 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. Default physiologies for infants with GA 25 to 40 weeks and PNA 2 days to 20 weeks were generated using built-in 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 simulated 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 *a priori* 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).

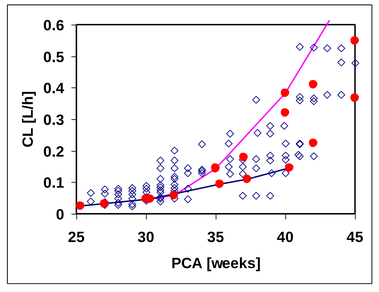


Figure 4: PBPK predicted (red dots) and PopPK fitted (blue dots) VCN renal clearance as a function of post-conceptional age (PCA = GA + PNA). Magenta line shows changes in VCN CL for GA = 30 weeks and varying PNA; blue line shows changes in VCN CL for PNA = 2 days and varying GA as predicted by PBPK model. Simulations were performed using default physiologies and GFR in GastroPlus for infants with varying GA and PNA, Fup and Rbp were scaled from adult values using the built-in scaling function in GastroPlus 9.0 based on age-dependent changes in plasma albumin levels and hematocrit.

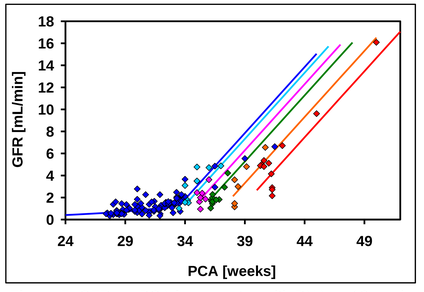


Figure 5: GFR vs. PCA for neonates with PNA up 12 weeks and GA = 27-33 weeks (blue), 34 weeks (cyan), 35 weeks (magenta), 36 weeks (green), 38 weeks (orange) and 40 weeks (red). GFR is increasing very slowly with GA during intrauterine development. For neonates born after at least 34 weeks of gestation, the GFR will start increasing rapidly immediately after birth. For neonates born before 34 weeks of gestation, the slow maturation of GFR from intrauterine development continues until ~34 weeks of PCA before the onset of the fast maturation phase. Lines represent built-in models in GastroPlus 9.0 [7] and points represent experimental data [7 and references therein]

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