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Prediction of Valsartan Pharmacokinetics in Pediatric Population using Physiologically Based Pharmacokinetic (PBPK) Model

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Aim

A method for transporter-based *in vitro-in vivo* extrapolation (IVIVE) was previously developed and demonstrated by predicting valsartan PK after *i.v.* administration [1]. The purpose of this study was to (1) extend the model to describe valsartan PK in human after *p.o.* administration, and (2) explore the utility of the model to predict valsartan PK in pediatric populations.

Methods

An absorption/PBPK model for valsartan PK was developed using GastroPlus™ 8.5 (Simulations Plus, Inc.). The program's Advanced Compartmental Absorption and Transit (ACAT™) model described the absorption of the drug, while PK was simulated with its PBPKPlus™ module. Physiologies were generated by the program's internal Population Estimates for Age-Related (PEAR™) Physiology™ module. Intestinal absorption and tissue distribution accounted for both passive diffusion and carrier-mediated transport. Total clearance consisted of biliary (major) and renal (minor) secretion. Passive diffusion between the extracellular and intracellular spaces in all tissues was calculated from specific permeability-surface area product (SpecPStc) and tissue cell volumes. SpecPStc along with the carrier-mediated transport kinetics in liver and kidney was predicted from previously reported *in vitro* measurements [2]. Passive renal secretion was estimated as Fup*GFR. Plasma protein and red blood cell binding was adjusted to account for pediatric plasma protein levels and hematocrit. The effect of intestinal MRP2 on valsartan absorption was included in the model. Model parameters (Vmax for liver, kidney and intestinal transporters, and SpecPStc) were also fitted against Cp-time profiles after *i.v.* and *p.o.* administration in adults [3], and the refined model was used to predict pediatric PK [4].

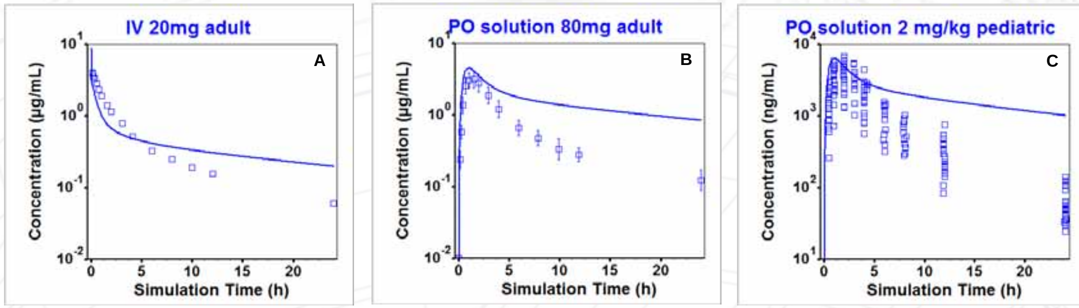

Figure 1: Predicted (lines) and observed (points) Cp-time profiles in adults after 20 mg *i.v.* (A) and 80 mg *p.o.* (B) administration and in children after 2 mg/kg *p.o.* administration. All predictions are based on average physiology (age and body weight) corresponding to the subjects from each study and *in vitro* values for carrier-mediated transport and passive diffusion through cell membranes. The expression levels of MRP2 in liver, kidney and gut were based on relative mRNA expression levels reported for these tissues [5]. The pediatric clinical trial included 1- to 15-year-old children (body weights in ranging from 9.3 to 192 kg). The simulated pediatric profile represents average physiology from the clinical trial (8-years-old, 50 kg).

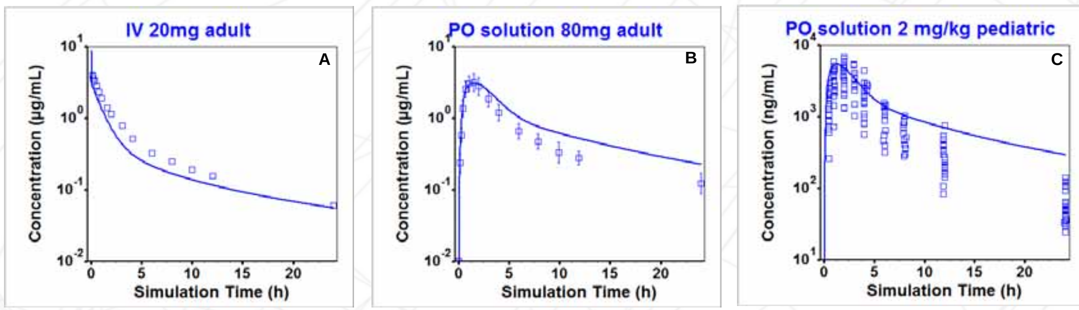

Figure 2: Simulated/predicted (lines) and observed (points) Cp-time profiles in adults after 20 mg *i.v.* (A) and 80 mg *p.o.* (B) administration and in children after 2 mg/kg *p.o.* administration. The adult data [3] were used to fit Vmax values for OATP and MRP2 transporters and Specific PStc value (the parameter used to calculate the passive diffusion through cell membranes in individual tissues). The model was then used to predict valsartan exposure in children [4]. The expression levels of MRP2 in liver, kidney and gut were based on relative mRNA expression levels reported for these tissues [5]. The pediatric clinical trial included 1- to 15-year-old children (body weights in ranging from 9.3 to 192 kg). The simulated pediatric profile represents average physiology from the clinical trial (8-years-old, 50 kg).

References

[1] Lukacova V., Poster presentation, 17th North American ISSX Meeting 2011, Atlanta, GA
[2] Poirier A. et al. J Pharmacokinet Pharmacodyn, 2009, 36: 585-611
[3] Flesch G. et al. Eur J Clin Pharmacol, 1997, 52: 115-120
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[5] Nishimura M. et al. Drug Metab Pharmacokinet 2005, 20(6): 452-477

Results

The initial model based on PEAR physiologies combined with *in vitro* estimates of transporter Km and Vmax values for liver transporters and Specific PStc gave reasonable predictions of valsartan exposure in adults and children (Cmax and AUC prediction errors ranged 20%-120%). A model refined against adult *in vivo* profiles resulted in much-improved prediction of pediatric exposure with less than 30% prediction error on both Cmax and AUC.

Table 1: Summary of *in vitro* and *in vivo* values describing carrier-mediated and passive valsartan distribution

Parameter	In vitro[a]	In vivo[b]
Specific PStc [mL/s/mL-cell vol]	0.00177	0.0006
OATP Km [ug/mL]	19.34	19.34
OATP Vmax [mg/s/mg-transp]	0.000159	0.00031
MRP2 Km [ug/mL]	19.34	19.34
MRP2 vmax [mg/s/mg-transp]	0.000159	0.0004

[a]- *in vitro* estimates of Km and Vmax values for MRP2 were not available and were set to the same values as OATP parameters (assuming that there is no drug accumulation in liver and biliary secretion rate would be at least the same as uptake into the liver).
[b]- Km values were not modified when fitting the model against the adult Cp-time profiles.

Conclusions

The transporter-based IVIVE method using SpecPStc showed adequate performance for prediction of pediatric PK from adult studies. The method extends the PBPK capabilities to predict pediatric exposure for compounds where PK cannot be described by the simpler, flow-limited, tissue models.

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