W5306

Prediction of Acyclovir Pharmacokinetics in Pediatric Populations using a Physiologically Based Pharmacokinetic (PBPK) Model

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

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

Aim

To develop a PBPK model for acyclovir incorporating processes affecting the drug's absorption and distribution after *i.v.* administration of acyclovir (ACV) as well as its *in vivo* formation after *p.o.* administration of the prodrug valacyclovir (VACV) in adults. Use the model to evaluate ACV pharmacokinetics in children.

Methods

A mechanistic absorption/PBPK model for VACV and ACV were developed using GastroPlus™ 8.5 (Simulations Plus, Inc.). The program's Advanced Compartmental Absorption and Transit (ACAT™) model described the absorption of both drugs, while PK for both was simulated with its PBPKPlus™ module. All physiologies were generated by the program's Population Estimates for Age-Related (PEAR™) Physiology™ module. Intestinal absorption and tissue distribution accounted for passive diffusion and carrier-mediated transport of both drugs. Total ACV clearance consisted of renal secretion (passive and carrier-mediated), biliary secretion, and metabolic clearance (Figure 1). VACV clearance consisted of metabolic conversion to ACV and passive renal filtration (Figure 1). A pH-dependent model accounted for the degradation rate of VACV in the gut lumen [1]. Passive diffusion through cell membranes in all tissues was calculated from specific permeability-surface area product (SpecPStc) for each drug along with tissue cell volumes [10].

Figure 1: Overview of critical processes determining the disposition of VACV and ACV in gut, liver, and kidney

SpecPstc and carrier-mediated Vmax in gut, liver, and kidneys for ACV were fitted against *in vivo* data (Cp-time profiles and urine data) after 1- and 6-hr *i.v.* infusions of ACV in adults [5]. Reported *in vitro* Km values were used for MATE1, MATE2K, OCT and OAT [2,3]. The model was validated by predicting ACV PK after 1-hr *i.v.* infusions of ACV doses ranging from 2.5 to 15 mg/kg [6].

SpecPstc, carrier-mediated uptake to gut, liver, and kidneys of VACV and metabolic conversion of VACV to ACV were fitted against Cp-time profiles of ACV after 100, 500 and 1000mg *p.o.* administration of VACV. Reported *in vitro* Km values were used for Valacyclovirase and PepT1 [1,4]. The model was validated by predicting ACV PK after 250 and 750mg *p.o.*administration of VACV [7].

ACV PK in different pediatric groups was predicted using drug-dependent parameters obtained from the adult model and known age-dependent physiological changes.

Results

The model provides excellent agreement with a variety of reported clinical profiles after *i.v.* administration of ACV and *p.o.* administration of VACV in adults (Figures 2-4).

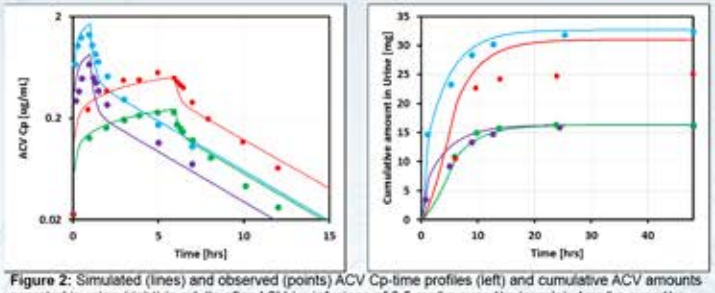

Figure 2: Simulated (lines) and observed (points) ACV Cp-time profiles (left) and cumulative ACV amounts secreted in urine (right) in adults after ACV *i.v.* infusions of 0.5 mg/kg over 1hr (purple); 1mg/kg over 1hr (blue); 0.5mg/kg over 6hrs (green); 1mg/kg over 6hrs (red). These datasets were used to fit ACV distribution and secretion parameters (SpecPstc and transporter Vmax values for ACV). Experimental data were obtained from [5].

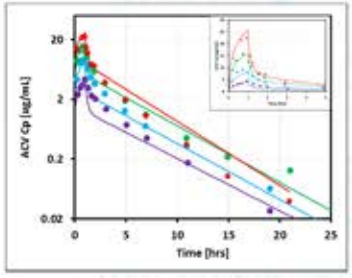

Figure 3: Predicted (lines) and observed (points) ACV Cp-time profiles after 1hr *i.v.* infusions of 2.5 mg/kg (purple), 5mg/kg (blue), 10mg/kg (green) and 15mg/kg (red) ACV. Predictions used the same model parameters as in simulations shown in Figure 1. Experimental data were obtained from [6]

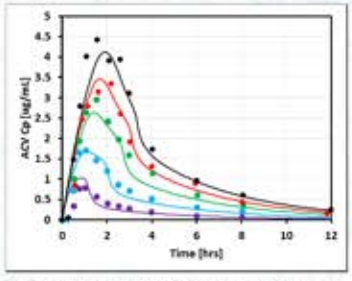

Figure 4: Simulated (lines) and observed (points) ACV Cp-time profiles after *p.o.* administration of VACV at doses 100, 250, 500, 750 and 1000mg. Profiles for 100, 500, and 1000mg doses were used to fit VACV disposition parameters (ACV disposition parameters were used as fitted for Figures 1 and 2). Profiles for 250 and 750 mg doses were predicted to further validate the model. Experimental data were obtained from [7]

A model calibrated against adult data provided reasonable predictions of ACV CL and Vd_{ss} for children from 1 to 17 years old. Vd_{ss} was predicted well even for infants (0-3 months old). CL was, however, overpredicted ~ 2.5-fold for this age group (Figure 5). This mismatch was expected due to the unknown ontogeny of transporters involved in ACV clearance.

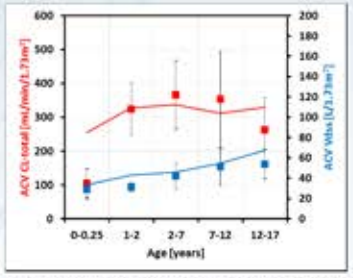

Figure 5: Predicted (lines) and observed (points) ACV total clearance (red) and volume of distribution (blue). Experimental data were obtained from [8].

Previously, we estimated the ontogeny of renal transporters from age-dependent changes of para-aminohippurate (PAH) tubular secretion and we successfully applied this method for the prediction of amoxicillin PK in neonates and infants [9].

Applying the same scaling for expression levels of renal transporters would result in predicted CL = 140 mL/min/1.73 m^2 for a 1-day-old newborn (transporters at 2% of adult levels) and CL = 240 mL/min/1.73m^2 for a 3-month-old infant (transporters at 30% of adult levels). Both predicted clearances are higher than the reported CL = 105 + 42 mL/min/1.73m^2 for a group of 0-3-month-old infants.

Scaling the OCT expression (liver influx transporter) by the same ratio as renal transporters results in predicted CL of 33 and 158 mL/min/1.73 m^2 for a 1-day-old newborn and a 3-month-old infant, respectively. The average CL = 95 mL/min/1.73m^2 is close to the reported average for this age group, suggesting similar rates of transporter maturation in both tissues. Further simulation studies are needed to verify (or modify) this hypothesis.

Conclusions

The power of PBPK models in predicting pediatric PK is dependent on the knowledge of age-dependent physiological changes. For many processes relevant to drug disposition, such information is not available. The current study presents a strategy for quantitating these changes from existing clinical data in children, and thus could improve the predictive ability of PBPK models for other compounds with similar *in vivo* fates.

References

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