R6366

Physiologically Based Pharmacokinetic (PBPK) Modeling of Amoxicillin Absorption and Pharmacokinetics

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Aim

Purpose of the study was to develop a PBPK model for amoxicillin incorporating saturable transport processes affecting the drug's absorption and distribution.

Methods

Amoxicillin absorption and pharmacokinetics were simulated using GastroPlus™ 8.0 (Simulations Plus, Inc., Lancaster, CA). The program's Advanced Compartmental Absorption and Transit (ACAT™) model described the passive and carrier-mediated absorption of the drug, while pharmacokinetics were simulated with its PBPKPlus™ module. Human organ weights, volumes, and blood perfusion rates were generated by the program's internal Population Estimates for Age-Related (PEAR) Physiology™ module. Individual tissues were represented as permeability-limited (diffusion-limited) models. Drug partitioning between plasma and extracellular tissue space accounted for drug binding to plasma proteins and extracellular tissue proteins [1]. Drug uptake into cells was modeled by passive diffusion, as well as carrier-mediated (saturable) transport in tissues expressing PepT1/PepT2 and MRP4 transporters (small intestine, kidney, liver, brain). Relative transporter expression levels in kidney, liver and brain were based on published relative mRNA expression levels in these tissues [2]. An additional uptake transporter was added to kidney tissue to account for active renal secretion of amoxicillin. Passive renal secretion was estimated from fraction unbound in plasma and glomerular filtration rate. Distribution kinetic parameters as well as liver and renal (active secretion) contributions to amoxicillin's clearance were fitted against plasma concentration-time (Cp-time) profiles and amounts secreted in urine after *i.v.* and *p.o.* administration of amoxicillin [3-5].

Results

A single model provides excellent agreement with a variety of reported clinical profiles (Cp-time profiles and cumulative amounts secreted in urine after *i.v.* administration of doses ranging from 250mg to 5g [3-4]; Cp-time profiles after *p.o.* administration of doses ranging from 375mg to 3g [5]) and accounts for the observed nonlinear dose-exposure relationship after *p.o.* administration of amoxicillin.

Table 1: Relative expression levels (mg-transporter/g-tissue) of PepT and MRP transporters in brain, kidney and liver used in simulation (based on published relative mRNA expression levels [2]). Values were normalized to PepT1/PepT2 expression in Kidney

	PepT1/PepT2	MRP4
Brain	0.835	0.324
Kidney	1	3.056
Liver	0.38	0.021

Table 2: Distribution kinetic parameters and clearance

	Km [mg/L]	Vmax [mg/s/mg-transp]
PepT1/PepT2 (kidney, liver, brain)	370#	0.0012
PepT1 (duodenum)	370#	0.09*
MRP4 (kidney, liver, brain)	687	0.02
Kidney influx	30	0.0008
Specific PStc [mL/s/mL-cell volume]		5.83E-6
Liver CL [L/h]		0.602

reported *in vitro* PepT2 Km [6] was used for interaction with PepT1 and PepT2, remaining parameters in Table 2 were fitted to *in vivo* data

* Vmax for PepT1 in duodenum is shown in mg/s; for remaining intestinal compartments, Vmax from duodenum was scaled using built-in relative PepT1 distributions along small intestine

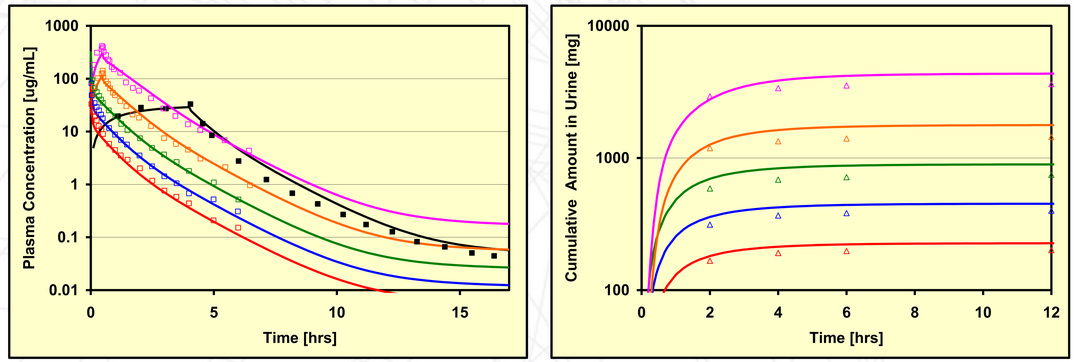

Figure 1: Simulated (lines) and observed (points) Cp-time (left) and urinary secretion (right) profiles of amoxicillin in healthy adult volunteers after *i.v.* administration of doses: 250mg bolus (red), 500mg bolus (blue), 1000mg bolus (green), 2g/30min infusion (orange), 5g/30min infusion (magenta), and 2g/4hr infusion (black).

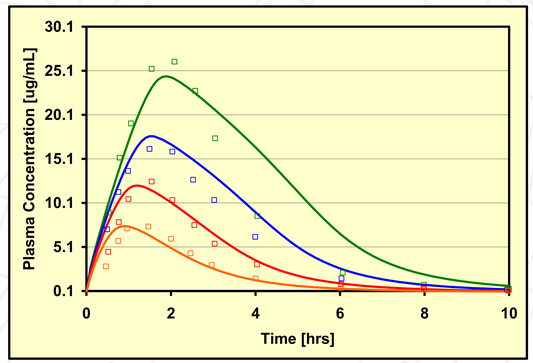

Figure 2: Simulated (lines) and observed (points) Cp-time profiles of amoxicillin in healthy adult volunteers after *p.o.* administration of doses: 375 mg (orange), 750 mg (red), 1500 mg (blue), and 3g (green).

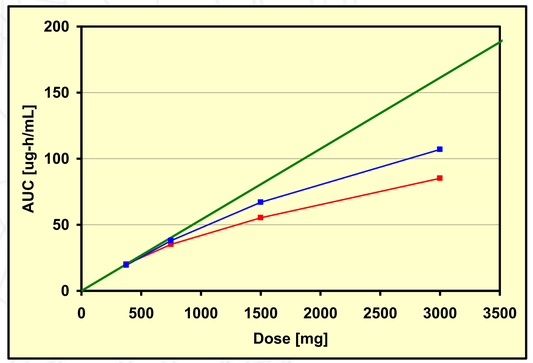

Figure 3: Simulated (blue) and observed (red) exposure-dose relationship for amoxicillin *p.o.* administration. Green line shows proportional dose-exposure relationship calculated from AUC of the lowest dose (375 mg).

Conclusions

Amoxicillin is eliminated primarily by renal secretion with a minor contribution from liver clearance (metabolism and biliary secretion). Its absorption, distribution, and clearance are affected by interactions with transporters. A fitted physiological model which includes relevant distribution mechanisms can be used to predict the drug's pharmacokinetics in different populations as well as potential transporter-based drug-drug interactions. Moreover, the development procedure of this model may serve as a recipe for building PBPK models for other compounds whose tissue distribution includes components of slow passive diffusion as well as carrier-mediated transport and cannot be described by the simpler perfusion-limited (flow-limited) tissue model.

References

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