Physiologically Based Pharmacokinetic (PBPK) Modeling of Amoxicillin in Neonates and Infants

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Objective:

An amoxicillin PBPK model was previously developed and validated in healthy adults as well as adults with altered renal function [1-2]. The purpose of this study was to explore the utility of the model in describing amoxicillin pharmacokinetics (PK) in neonates and infants.

Methods:

An adult absorption/PBPK model for amoxicillin was previously developed [1] using GastroPlus™ 8.0 (Simulations Plus, Inc., Lancaster, CA). The program's Advanced Compartmental Absorption and Transit (ACAT™) model described the absorption of the drug, while PK was simulated with its PBPKPlus™ module. In the adult model, both intestinal absorption and tissue distribution included passive diffusion and carrier-mediated transport (PepT1/PepT2 influx and MRP4 efflux in kidney, liver and brain; PepT1/PepT2 influx in intestine; and a basolateral influx transporter in kidney). Total clearance consisted of renal (major) and hepatic (minor) components. Physiological parameters were generated by the program or obtained from literature. Certain drug-dependent parameters were obtained by fitting against reported plasma concentration-time (Cp-time) profiles and amounts secreted in urine after amoxicillin *i.v.* and *p.o.* administration in healthy volunteers. The model was further validated by predicting amoxicillin PK in different adult populations [2]. For this study, infant and neonate physiologies were based on information collected from literature. Aside from body weight, height, and individual tissue sizes and blood flows, parameters with a large effect on amoxicillin pharmacokinetics included changes in extracellular water in very young infants, glomerular filtration rate, and renal transporters. Fraction unbound in plasma and blood-to-plasma concentration ratio were adjusted to account for infant plasma protein levels and hematocrit. Literature information on ontogeny of relevant transporters was not found. The PBPK model, along with observed amoxicillin Cp-time profiles after *i.v.* administration, was used to estimate transporter expression levels in different groups of infants.

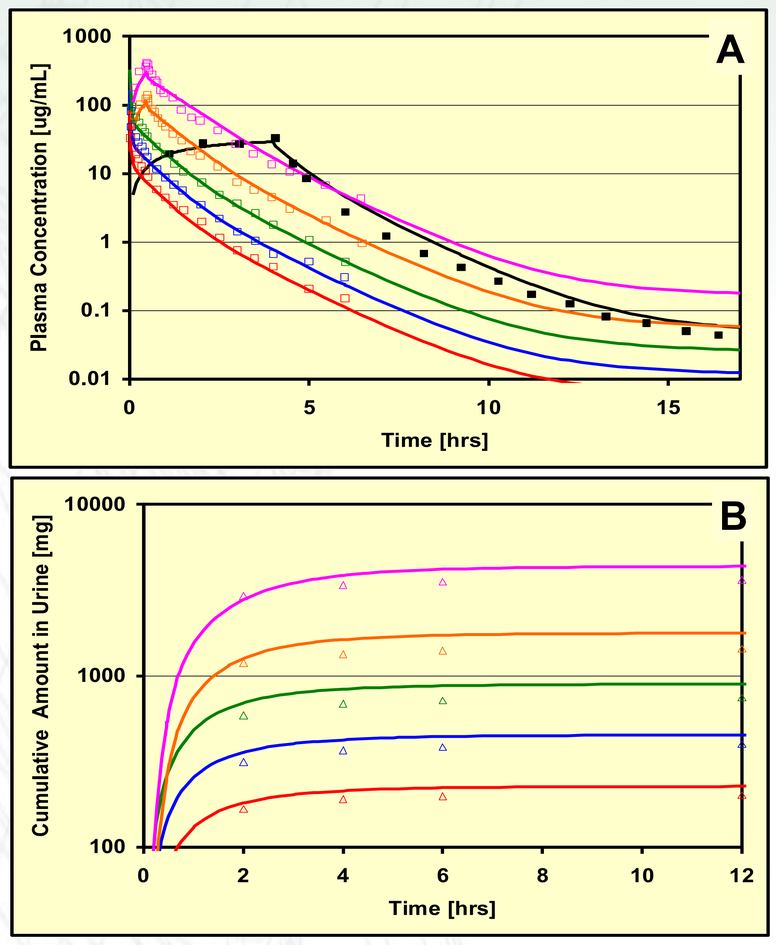

***Figure 1**: Simulated (lines) and observed (points) Cp-time (A) and urinary secretion (B) profiles of amoxicillin in healthy adult volunteers after i.v. administration of doses: 250mg bolus (red), 500mg bolus (blue), 1000mg bolus (green), 2g/30min infusion (orange), 5g/30min infusion (magenta), and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

Results:

The previously developed adult PBPK model for amoxicillin correctly predicted amoxicillin volume of distribution in neonates and infants after incorporating physiological parameters relevant for this population, i.e., tissue sizes, extracellular water volume, and slow passive diffusion across tissue membranes. In adults, the renal clearance consisted of contributions from both passive glomerular filtration and active tubular secretion. In this study, the glomerular filtration rate (GFR) was incorporated as reported in the literature for different ages of full-term and pre-term infants [3-6]. Transporter expression levels were fitted against observed Cp-time profiles from some studies and validated by simulating amoxicillin PK in subjects of similar age from different studies.

Results for the youngest group (1-3-day-old neonates born on average 11 weeks premature) are shown in Figure 2. The data after 25mg/kg *i.v.* administration [7] was used to scale transporter levels (Figure 2A). The resultant model was then used to predict amoxicillin PK after 50mg/kg *i.v* administration (Figure 2B) from a different study [8]. Both the GFR estimated from literature data [3-6] and fitted transporter levels were very low for these premature neonates: estimated GFR was ~10% of the adult value (when expressed per 1.73m^2), while fitted transporter levels per g of tissue were 2% of adult levels.

Results for *i.v.* doses of 14.8 - 41.5 mg/kg in older infants and children (10-months to 3 years old) are shown in Figure 3. The GFR estimated from literature data [3-6] was 85% and 115% of the adult value (when expressed per 1.73m^2) for 10-12-month-old and 3 year-old children, respectively. Fitted transporter levels per g tissue were 30% of adult values for all three groups.

The differences in scaling for GFR and transporter levels are in line with the reported different rates of maturation of GFR and active tubular secretion [7]. The final model was used to explore potential sources of observed variability in amoxicillin PK in infants (Figure 4).

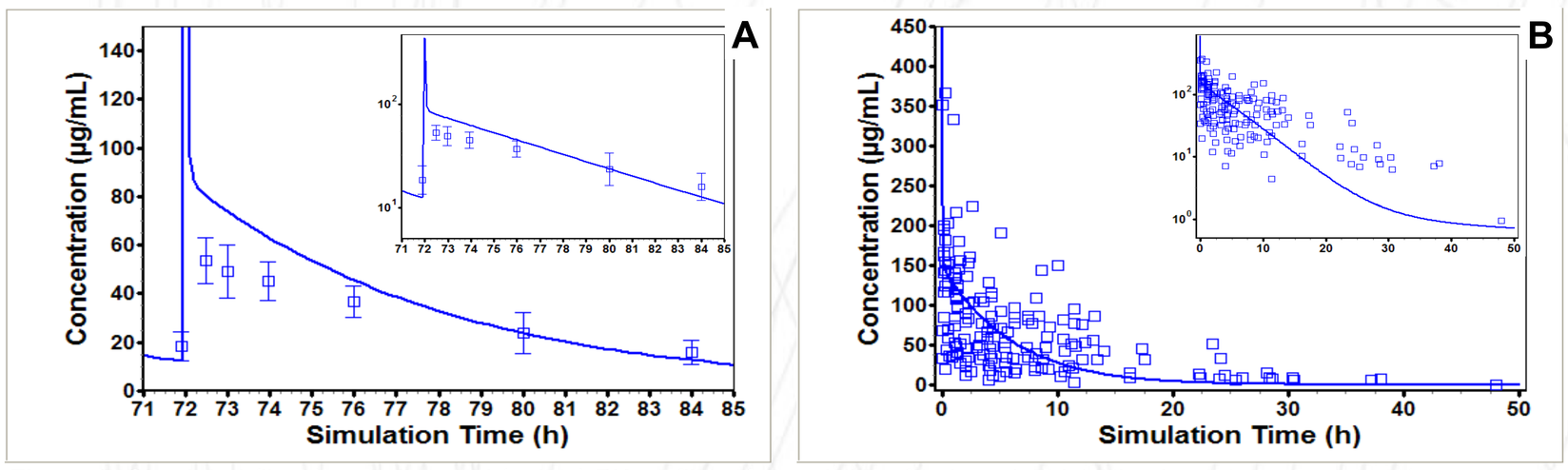

***Figure 2.** Simulated (lines) and observed (points) PK profiles of amoxicillin after i.v. administration in preterm neonates (average gestational age 29 weeks). A) 25mg/kg dose on day 3 after birth (observed data are from [7]), B) 50mg/kg dose on days 1-3 after birth (observed data are from [8])*

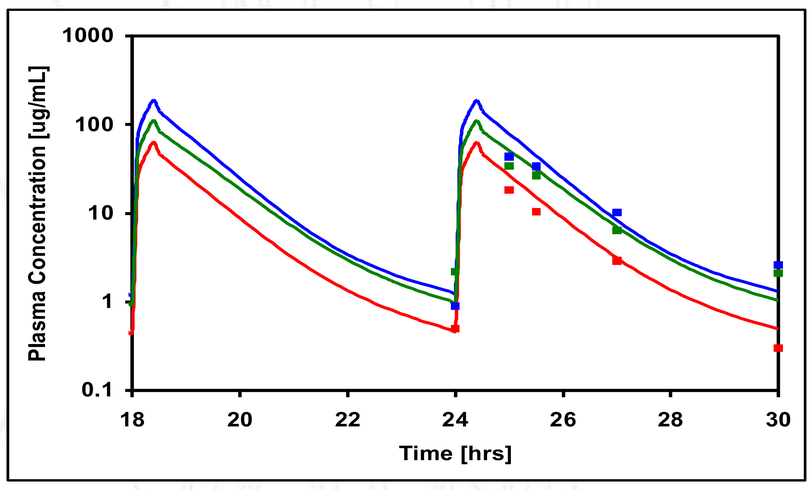

***Figure 3.** Simulated (lines) and observed (points) PK profiles of amoxicillin after i.v. administration in 16-month-old infants (14.8 mg/kg, red); 10-month-old infants (26.4 mg/kg, green); 3-year-old children (41.5 mg/kg, blue). Observed data are from [9].*

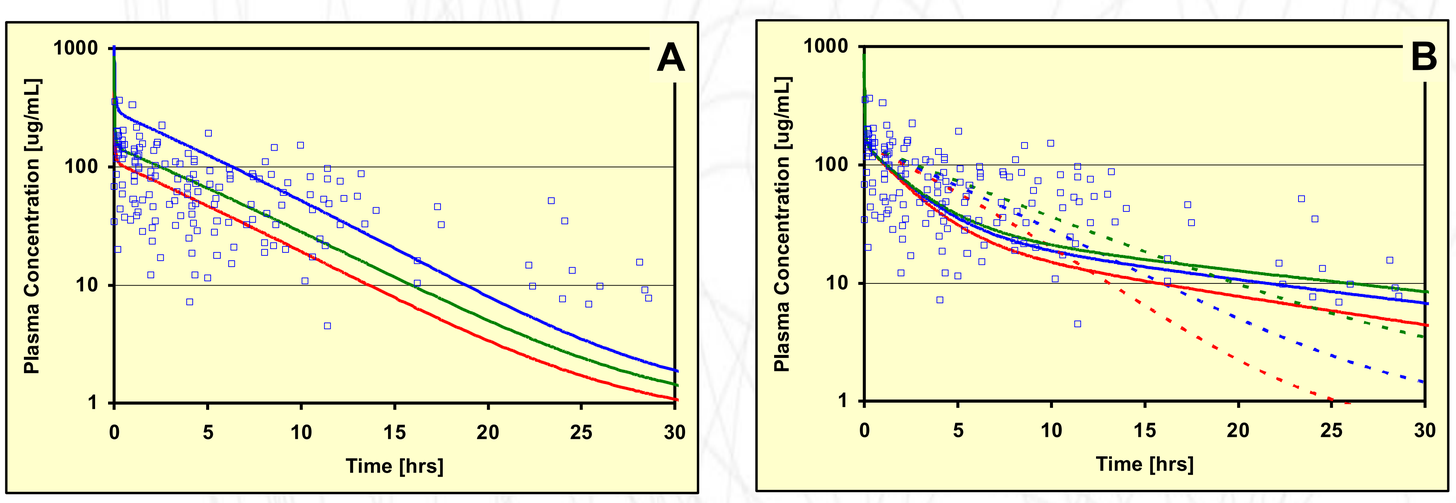

***Figure 4.** Effects of gestational age, passive membrane diffusion and transporter expression levels on amoxicillin PK in 2-day-old neonates. A) Simulations for neonates born 16 (blue), 11 (green) and 8 (red) weeks premature. All three simulations used permeability across tissue membranes (P_{eff}) as obtained from adult model and transporter levels at 2% of adult values. B) Simulations for neonates born 11 weeks premature with transporter expression levels at 1% (green), 2% (blue) and 4% (red) of adult values and P_{eff} as obtained from adult model (dotted lines) and 10-fold higher than in adults (solid lines). In all simulations, the rate coefficient for passive diffusion across tissue membranes (PStc) was calculated as [P_{eff} * Surface area of tissue cell membranes], where surface areas were automatically scaled based on physiology for each tissue. Observed data from [8] are shown for comparison.*

Conclusions:

Amoxicillin is eliminated primarily by renal secretion with a minor contribution from liver clearance (metabolism and biliary secretion).
A physiological model that included relevant distribution and clearance mechanisms was previously fitted and validated against data for different adult populations. In the current work, the model was applied to simulations of amoxicillin PK in neonates and infants: (1) to fill in missing pieces of physiological information (scaling of transporter expressions) using available *in vivo* data which could be used to predict PK of similar drugs; and (2) to explore sources of variability in amoxicillin PK in young children and provide useful insights into the drug's behavior in populations where large scale clinical studies are not feasible.

References:

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