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Prediction of Amoxicillin Pharmacokinetics in Populations with Altered Renal Function

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Aim

Purpose of the study was to predict amoxicillin pharmacokinetics in populations with altered renal function to further validate an absorption/PBPK model for amoxicillin.

Methods

An absorption/PBPK model for amoxicillin was developed 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. Both intestinal absorption and tissue distribution included components of passive diffusion and carrier-mediated transport. Total clearance consisted of renal (major) and hepatic (minor) components. Physiological parameters (tissue sizes, blood flows, relative expression levels of transporters, etc.) were generated by the program or were obtained from literature. A number of 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. To verify that the model included correct contributions of different processes affecting the Cp-time profile, the model was used to predict the amoxicillin pharmacokinetics in different populations. In this prediction, renal clearance was adjusted according to reported changes in renal function in pregnant women and in subjects with impaired renal function. The remaining fitted drug-dependent parameter values were retained as fitted earlier against Cp-time profiles in healthy volunteers.

Conclusions

Amoxicillin is eliminated primarily by renal secretion with only a minor contribution from liver clearance, so a good correlation between amoxicillin exposure and renal function was expected. However, the model was developed primarily utilizing Cp-time and urine secretion profiles and included a number of processes (absorption, distribution, renal and hepatic clearance) that affect these quantities. Reasonably accurate predictions of amoxicillin pharmacokinetics in populations that were not considered during model development further validated the model.

Results

Utilizing only reported information about physiological changes relevant for disposition and clearance of renally secreted compounds during pregnancy, the same model that was built on healthy subjects who were not pregnant correctly predicted differences in amoxicillin exposure after *p.o.* administration in pregnant women in their second and third trimester as well as postpartum. Similarly good predictions were obtained for patients with varying degrees of renal impairment.

Pregnancy:

Physiologies for typical healthy women were generated and subsequent adjustments were made to venous and arterial blood volumes (based on reported changes in plasma volume [1] and hematocrit [1-2] during pregnancy), glomerular filtration rate (GFR, based on reported changes in inulin clearance [2] during pregnancy), active renal secretion (based on reported changes in para-aminohippurate (PAH) clearance [2] during pregnancy).

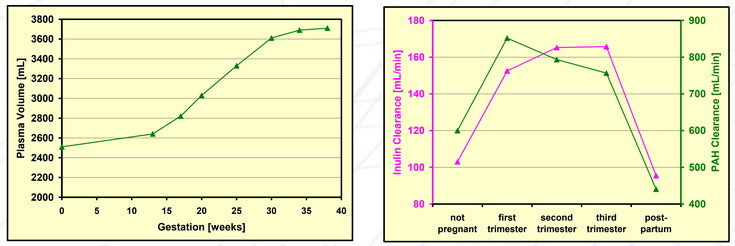

Figure 1: Physiological changes in plasma volume and renal secretion during pregnancy.

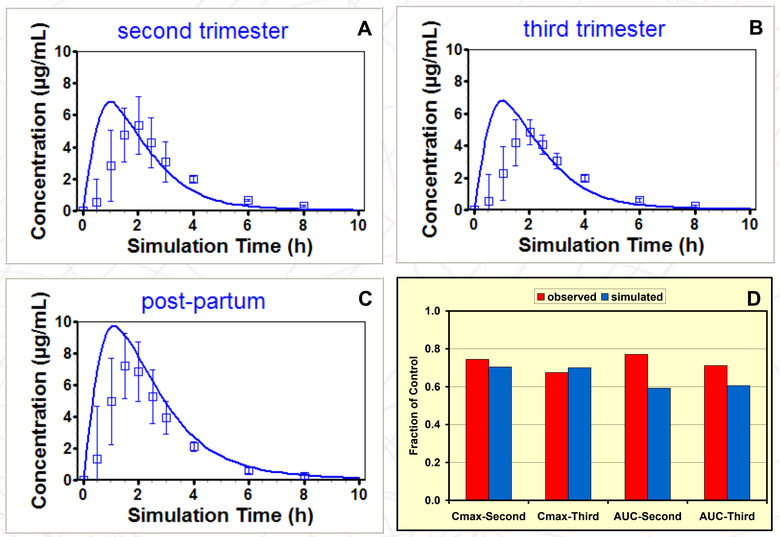

Figure 2: Predicted (lines) and observed (points) Cp-time profiles of amoxicillin after 500mg *p.o.* dose in different stages of pregnancy (A-C) and summary of predicted changes in exposure during second and third trimester compared to control where post-partum exposure was used as control (D). Observed data were obtained from literature [3]. Simulations were not refitted to the data, but were used as developed for healthy, nonpregnant women, adjusting only for reported changes in plasma volume and renal secretion during pregnancy as illustrated in Figure 1.

Renal impairment:

Physiologies for typical healthy males of corresponding age were generated for each group of subjects for which amoxicillin PK was reported [4]. Subsequent adjustments were made to GFR based on the reported average creatinine clearance for each group. Changes in active tubular secretion for these subjects were not reported and we assumed that active secretion would be affected in a similar way as passive filtration. Expression levels of renal transporters were adjusted by the same ratio as the ratio of reported GFR for each group and typical GFR for a given age.

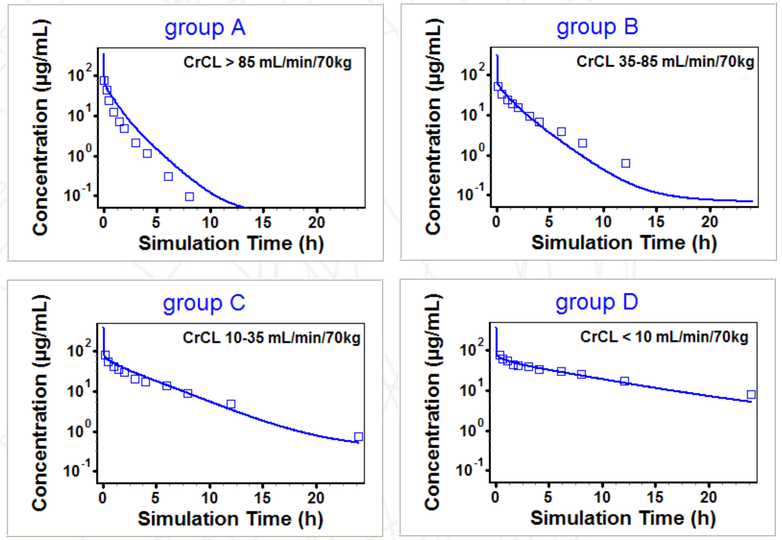

Figure 3: Predicted (lines) and observed (points) Cp-time profiles of amoxicillin after *i.v.* administration (1g bolus dose) in subjects with different degrees of renal impairment. Observed data were obtained from literature [4]. Simulations were not refitted to the data, but were used as developed for healthy males, adjusting only for reported changes in renal clearance.

References

1. Silversides C.K; Physiological Changes in Pregnancy, In: Heart Disease in Pregnancy, Eds. Oakley C. & Warnes C.A., Wiley, 2007
2. Sims E.A.H.; J Clin Invest 1958, 37: 1764-1774
3. Andrew M.A.; Clin Pharmacol Ther 2007, 81: 547-556
4. Humbert G.; Antimicrob Agents Chemother 1979, 15: 28-33

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