Semi-mechanistic Population Pharmacokinetic Modeling of Cefadroxil: An Example of PEPT2-mediated Renal Tubular Reabsorption

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Purpose
PEPT2, a proton-coupled oligopeptide transporter, plays a primary role in the renal tubular reabsorption of some drugs including the antibacterial agent cefadroxil which is essentially excreted unchanged in the urine of mice. The systemic clearance of cefadroxil is significantly higher in PEPT2 null mice than in wild-type mice due to depletion of this protein. The aim of this study was to characterize the pharmacokinetics of cefadroxil in wild-type and PEPT2 null mice using non-linear mixed effects modeling (NONMEM).

Methods
Pharmacokinetic data of cefadroxil in wild-type and PEPT2 null mice following intravenous administration (doses ranged from 1 - 100 nmol/g) were analyzed using NONMEM 7.2. Different models with linear and/or nonlinear elimination kinetics were then examined. The final model was selected based on the likelihood ratio test, visual inspection of diagnostic plots and evaluated by visual predictive check.

Results
The pharmacokinetic profile of cefadroxil was best described by a two-compartment model with linear renal elimination (i.e., filtration and tubular secretion) and nonlinear tubular reabsorption (mediated by PEPT2) in wild-type mice, whereas, only linear renal elimination (i.e., filtration and tubular secretion) was considered in PEPT2 null mice. The nonlinear kinetics of PEPT2-mediated tubular reabsorption was well characterized by the Michaelis-Menten parameters Vmax = 0.08±0.03 nmol/min/g and Km = 9.1±4.0 μM. These results are consistent with previously reported PEPT2 transport kinetics (i.e., Km = 10 - 40 μM).

Conclusion
In the present study, we demonstrated that the pharmacokinetics of cefadroxil was well characterized by a model that incorporated linear renal elimination along with nonlinear PEPT2-mediated tubular reabsorption in mice. This population pharmacokinetic model may help to provide mechanistic insight into the predominant role of PEPT2 in renal tubular reabsorption of cefadroxil and facilitate the prediction of cefadroxil disposition in human.

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