Using PBPK Modeling to Predict the Effect of Renal Transporter Inhibition by Probenecid on the Pharmacokinetics of Three Renally-Cleared Drugs

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Purpose
To explore the utility of physiologically-based pharmacokinetic (PBPK) modeling, with a mechanistic kidney framework, in predicting the effect of competitive transporter inhibition on the pharmacokinetics of three renally-cleared drugs.

Methods
Three substrate drugs—oseltamivir carboxylate (OC), cidofovir and cefuroxime—were chosen based on the criteria that they are all predominantly renally cleared with active secretion and that their exposures were increased when probenecid was co-administered in humans. PBPK models of each drug were developed using population-based PBPK software Simcyp® (V12.1). Drug-dependent parameters were derived from a medley of in silico, in vitro, and in vivo sources. System-dependent parameters utilized existing “Healthy Volunteers” population data within Simcyp. A general modeling approach assumed that a single basolateral uptake transporter and a single apical efflux transporter describe the net kidney uptake and net efflux, respectively. Transporter-mediated clearances were determined based on systemic (for basolateral uptake) and urine data (for apical efflux). Probenecid was selected as the perpetrator drug to inhibit the basolateral uptake transporter defined in the substrate models. Probenecid model development followed the same approach except for the use of a saturable hepatic clearance. The effect of competitive drug-drug interaction (DDI) was investigated by conducting sensitivity analyses on a range of probenecid Ki values. The resulting predicted AUCRs+Inh/-Inh (AUC with probenecid interaction: AUC without probenecid interaction) were then compared to observed AUCRs from in vivo DDI studies.

Results
PBPK modeling suggested that probenecid Ki values toward uptake transport appeared to be ~1 µM for OC and cidofovir, and ~10 µM for cefuroxime, in order to predict the observed AUCRs from clinical studies. These values are within the same magnitude as reported for probenecid in vitro inhibition potency (Ki 1-30 µM against organic anion transporter OAT).

Conclusion
The effect of probenecid on basolateral uptake of three renally-cleared drugs was evaluated using PBPK. The model-derived Ki value of ≤1 µM under current model structure may be used conservatively to predict probenecid’s inhibition effect on renal uptake transport by OATs. Higher Ki for cefuroxime PBPK model suggested an additional contribution of renal uptake transporter(s) that may not be effectively inhibited by probenecid.