Exploration of the interplay between enterohepatic circulation (EHC) and transport: a physiologically-based pharmacokinetic (PBPK) modeling approach using pravastatin and rosuvastatin as model drugs

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Objectives: The pharmacokinetics of pravastatin (PRA) and rosuvastatin (ROS) is dependent intestinal efflux, hepatic uptake and biliary efflux. Contribution of EHC to PRA and ROS disposition further confounds identifiability of these clearance pathways. This work aimed at developing a PBPK modeling approach to address EHC-dependent identifiability issues, allowing the use of this model to predict DDIs for agents with similar complex disposition.

Methods: Full PBPK (with ADAM absorption) models for PRA and ROS were developed in SimCYP (v.14) using available physicochemical, in vitro transport and in vivo renal clearance values based on observed single oral dose clinical data for PRA and ROS in the absence of DDIs. Scaling factors for tissue partitioning (SF_{VD}), hepatic uptake (SF_{HU}) and intestinal efflux (CL_{GE}) were evaluated over 0-100% range of percent of drug reabsorbed (%RA) and optimized based on OFV nadir. The optimized models were then evaluated for their ability to predict observed DDIs with PRA and ROS in the presence of inhibitors of intestinal efflux, hepatic uptake, and biliary efflux.

Results: For PRA and ROS, a %RA of 0% and 50%, respectively, best fit the plasma concentration curves in the absence of DDIs. Increasing %RA from 0 to 100% increased the estimated SF_{HU} approximately 3-fold for PRA (SF_{HU}=28-83) and ROS (SF_{HU}=46-143), resulting in a maximal AUC ratio (due to hepatic uptake inhibition) from 4-9 and 10-27, respectively; consistent with clinical data. Intestinal efflux-to-permeability clearance ratios were large for ROS (range: 7-28) and smaller for PRA (range: 0.2-2). Despite large predicted increases in PRA and ROS C_{max} (~10-fold), AUC'/AUC after inhibiting gut efflux was minimal; consistent with near complete absorption.

Conclusions: Using PRA and ROS as model drugs, the described sensitivity-estimation method can predict the presence and extent of human EHC. EHC should be accounted for model development because it significantly affects transporter clearance estimates and predicted transporter inhibition liability.