Physiologically Based Pharmacokinetic Modeling of Rosuvastatin and Prediction of Transporter-Mediated Drug-Drug Interactions Involving Gemfibrozil

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PURPOSE

Rosuvastatin (Crestor®) is a commonly prescribed lipid-lowering agent from the statin drug class for the treatment of primary hyperlipidemia and hypertriglyceridemia. It may be coprescribed with another lipid-lowering drug such as gemfibrozil due to their complementary effect. Rosuvastatin is a substrate of multiple transporters including organic anion transporting polypeptides 1B1 (OATP1B1), 1B3 (OATP1B3), 2B1 (OATP2B1), as well as sodium-taurocholate cotransporting polypeptide (NTCP) and breast cancer resistance protein (BCRP), and exhibits minor metabolic clearance. Gemfibrozil is an inhibitor of the OATP1B1 transporter, which accounts for ~50% of the active liver uptake clearance of rosuvastatin. Studies have reported that concomitant administration of statins and gemfibrozil is associated with an increased risk of myopathy and rare but life-threatening rhabdomyolysis, possibly caused by increased systemic exposure of statins. Patients with genetic polymorphisms may be at a higher risk of severe drug interactions when rosuvastatin and gemfibrozil are coprescribed. The objective of this study was to develop a physiologically based pharmacokinetic (PBPK) model of rosuvastatin following oral administration, and to apply this model to predict the transporter-mediated drug-drug interactions with gemfibrozil.

METHODS

- The GastroPlus™ 9.0 (Simulations Plus, Inc.) Advanced Compartmental Absorption and Transit™ (ACAT™) model was used in conjunction with the PBPKPlus™ and Metabolism and Transporter modules to build a mechanistic absorption/PBPK model for rosuvastatin.
- Physicochemical and biochemical parameters that predict absorption and distribution were obtained from literature [1] or were predicted from structure with ADMET Predictor™ 7.2 (Simulations Plus, Inc.).
- Human organ weights, volumes, and blood perfusion rates were generated by the Population Estimates for Age-Related (PEAR™) Physiology™ module.
- All tissues except the liver were modeled as perfusion-limited tissues. Tissue/plasma partition coefficients (Kps) of perfusion-limited tissues were calculated using the Berezhkovskiy method [2] based on tissue composition and *in vitro* and *in silico* physicochemical properties.
- Intestinal passive absorption, BCRP-mediated active efflux, and enterohepatic circulation of rosuvastatin were incorporated in the PBPK model. The permeability-limited liver model included active sinusoidal uptake, passive diffusion, metabolism, and biliary secretion mediated by active canalicular efflux (**Figure 1**).
- *In vitro* Km values for OATP1B1, OATP1B3, NTCP and BCRP transporters were obtained from literature [3-5]. V_{max} values for the liver uptake transporters were fitted against *in vivo* data to match estimated contribution of each transporter (~50% for OATP1B1, ~35% for NTCP and ~16% for OATP1B3) to the total active hepatic uptake of rosuvastatin [5-6].
- The model was validated by comparing simulated and observed plasma concentration-time profiles for parent drug across several different dose levels following single and multiple oral administrations obtained from literature [7-12].
- Intestinal passive absorption and metabolic clearance both in gut (CYP3A4) as well in permeability-limited liver (CYP3A4 and UGT2B7) were included in gemfibrozil model. MRP transporter-mediated biliary secretion, renal clearance, enterohepatic circulation and parent to metabolite interconversion were incorporated in disposition of gemfibrozil glucuronide metabolite.
- OATP1B1 and NTCP transporter-mediated drug-drug interactions were predicted with the GastroPlus DDI module through dynamic simulations using the validated rosuvastatin and gemfibrozil PBPK models
- IC_{50} for gemfibrozil inhibition of rosuvastatin OATP1B1- and NTCP-mediated liver uptake was from the literature [5,10]

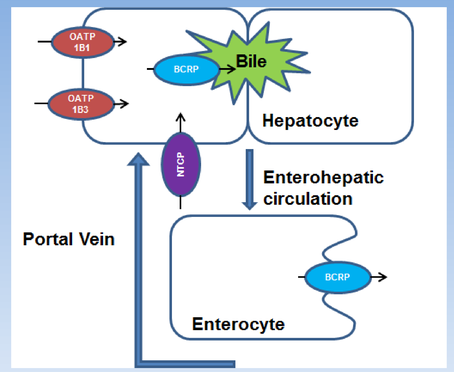

Figure 1. Overview of the major processes governing the disposition of rosuvastatin in gut and liver.

RESULTS

- The model adequately described hepatobiliary disposition and dose proportional pharmacokinetics of rosuvastatin over the dose range of 10 to 80 mg in different populations of subjects following an oral administration (**Figure 2A, B, C and D**)

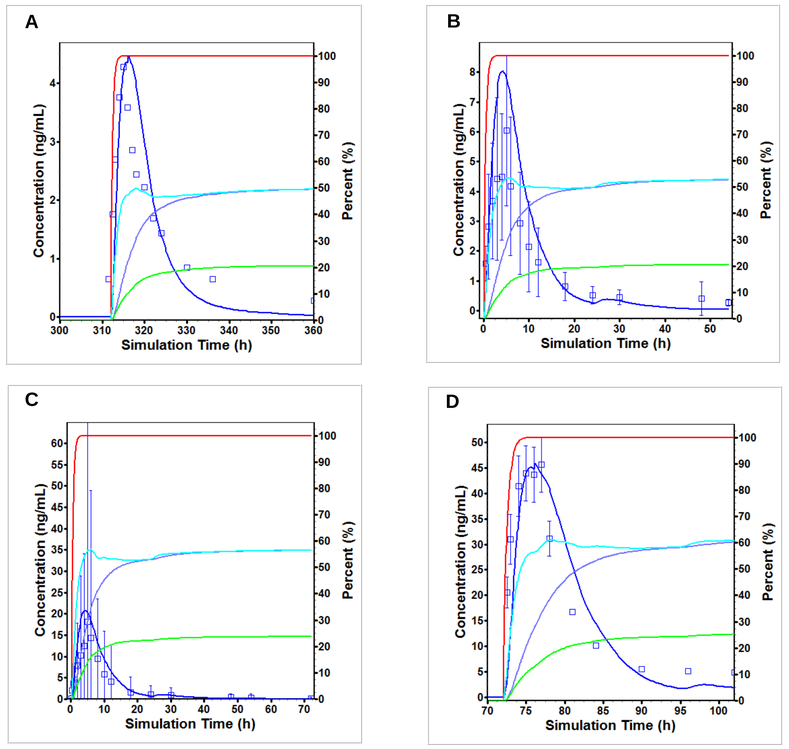

Figure 2. Observed (points) and simulated (lines) plasma concentration-time profiles of rosuvastatin after multiple doses of 10 mg (A), single dose of 20 mg (B), single dose of 40 mg (C), and single dose of 80 mg (D) in healthy volunteers. Experimental data were obtained from literature [7-10]. Amount dissolved (red), amount absorbed (cyan) cumulative amount that entered portal vein (blue) and cumulative amount that entered systemic circulation (green).

- The simulated AUC_{0-t}, C_{max} and t_{max} values were within 1.5-fold of the observed data following (10-80 mg) oral doses of rosuvastatin.
- The predicted increase in plasma AUC_{0-t} and C_{max} of rosuvastatin in the presence of gemfibrozil was approximately 2-fold, which was in close agreement with observed values [5] as shown in **Table 1** and **Figure 3A**.
- The inhibitory effect of gemfibrozil on activity of uptake transporters resulted in identical fold change in AUC_{0-t} and C_{max} of muscle and plasma (**Figure 3B)**.

C_{max} Ratio			AUC Ratio		
Observed	Predicted		Observed	Predicted	
Plasma	Plasma	Muscle	Plasma	Plasma	Muscle
2.21	2.13	2.12	1.88	1.95	1.95

Table 1. Summary of observed and predicted DDI of rosuvastatin with gemfibrozil.

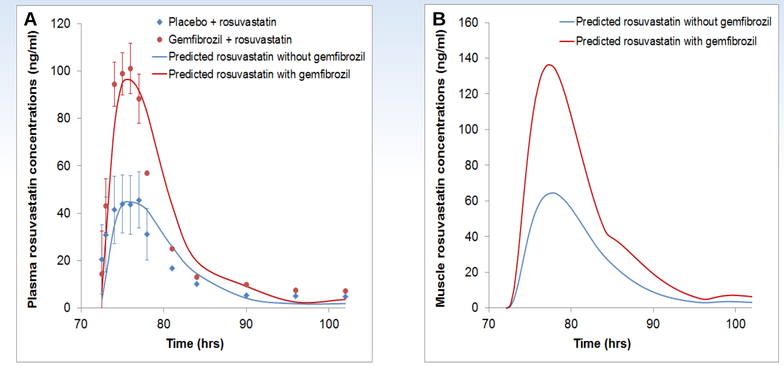

Figure 3. Observed (points) and simulated (lines) plasma (A) and muscle (B) concentration-time profiles of rosuvastatin after an oral dose of 80 mg with oral gemfibrozil pretreatment (600 mg twice daily for 7 days) or placebo. Experimental data were obtained from the literature [10].

CONCLUSIONS

- The absorption and pharmacokinetics of rosuvastatin were accurately modeled using only *in vitro* data. The model successfully predicted the drug-drug interaction related to inhibition of OATP1B1- and NTCP-mediated rosuvastatin hepatic uptake by gemfibrozil.
- Increased muscle levels of rosuvastatin upon concomitant administration of gemfibrozil may explain high risk of muscle-related side effects.
- This model can be extended for quantitative prediction of the impact of genetic polymorphisms and drug-drug interactions mediated by OATP, NTCP, and BCRP inhibitors.
- The model can help to identify populations at increased risk for side effects and to optimize their dosing regimens for the safe and effective use of rosuvastatin.

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