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 class for the treatment of primary hyperlipidemia and hypertriglyceridemia. It may be co-prescribed 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 co-prescribed. 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 permeable-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]. Vmax 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 as 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.

IC50 for gemfibrozil inhibition of rosuvastatin OATP1B1- and NTCP-mediated liver uptake was from the literature [5,10].

RESULTS

The model adequately described hepatic 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).

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

<table>
<thead>
<tr>
<th>drug</th>
<th>observed (AUC, %)</th>
<th>predicted (AUC, %)</th>
<th>observed (AUC, %)</th>
<th>predicted (AUC, %)</th>
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<tr>
<td>plasma</td>
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<td>2.12</td>
<td>1.88</td>
</tr>
<tr>
<td>muscle</td>
<td>1.95</td>
<td>1.95</td>
<td>1.95</td>
<td>1.95</td>
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</tbody>
</table>

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 vivo 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.

REFERENCES