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

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PURPOSE
Statins have been extensively used worldwide for the treatment of cardiovascular diseases. However, compliance which is a key for the best treatment outcomes is the issue due to the side effects. Understanding the underlying mechanisms involved in the disposition of statins is required for optimal dosing to improve compliance. PBPK modeling approach allows to investigate and identify the underlying mechanisms to better understand ADME processes and determinants of drug interactions. Rosuvastatin (Crestor®) is a commonly prescribed lipid-lowering agent from the statins class for the treatment of primary hyperlipidemia and hypertriglycerideremia. Rosuvastatin is a substrate for multiple transporters including organic anion transporting polypeptides (OATP1B1 and OATP1B3), sodium-taurocholate cotransporting polypeptide (NTCP), breast cancer resistance protein (BCRP), and exhibits minor metabolic clearance. The objective of this study was to develop a physiologically based pharmacokinetic (PBPK) model of rosuvastatin and to apply this model to predict the transporter-mediated drug-drug interactions (DDIs) with rifampicin, which is an inhibitor of multiple drug transporters.

METHODS
The GastroPlus® 9.7 (Simulations Plus, Inc., Lancaster, CA) Advanced Compartimental 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 biopharmaceutical properties that predict absorption and distribution were obtained from literature [1] or were predicted from structure with ADMET Predictor™ 9.5 (Simulations Plus, Inc., Lancaster, CA). Human organ weights, volumes, and blood perfusion rates were generated by the Population Estimates for Age-Related (PEAR™) Physiology™ module.

RESULTS
➢ The PBPK model adequately described C-time profiles of rosuvastatin for a variety of doses after i.v. and p.o. administration in different populations of subjects (Figure 2A, B, C and D).

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

Figure 2. Observed (points) and simulated (lines) plasma concentration-time profiles of rosuvastatin after 8 mg i.v. infusion (A), single oral dose of 10 mg (B), 40 mg (C), and 80 mg (D) in healthy volunteers. Experimental data were obtained from literature [7,9]. Cumulative amount dissolved (red), absorbed (cyan), entered portal vein (blue), and entered systemic circulation (green) are all shown on right Y-axis as percent of administered dose.

➢ The predicted DDI effect, fold increase in rosuvastatin plasma AUC0-24 and Cmax due to rifampicin coadministration, was within two-fold of the observed DDI effect [10] as shown in Table 1. The interaction is predicted very accurately for 600 mg p.o. rifampicin (~5% prediction error) but underpredicted (1.5 – 1.9-fold) with 30 min i.v. infusion of 600 mg rifampicin (Figure 3A and 3B).

➢ Magnitude of interactions was underpredicted with relative contribution of hepatic uptake transporters of rosuvastatin: ~50% OATP1B1, ~35% NTCP, and ~15% OATP1B3 estimated from vitro studies [11]. The interactions were better predicted with reassignment of relative contribution: ~70% OATP1B1, ~10% NTCP, and ~20% OATP1B3 [12].

➢ Oral rifampicin inhibited intestinal efflux by BCRP which resulted in increased gut absorption. The inhibition effect of rifampicin on MRPS efflux transporter in kidney had no effect on rosuvastatin pharmacokinetics.

Table 1. Summary of observed and predicted DDIs of rosuvastatin with rifampicin.

<table>
<thead>
<tr>
<th>Cmax Ratio</th>
<th>AUC0-24 Ratio</th>
<th>Observed</th>
<th>Predicted</th>
<th>Observed</th>
<th>Predicted</th>
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<tbody>
<tr>
<td>p.o. rifampicin</td>
<td>5.51</td>
<td>3.65</td>
<td>4.55</td>
<td>2.39</td>
<td></td>
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<tr>
<td>i.v. rifampicin</td>
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<td>9.49</td>
<td>5.24</td>
<td>5.45</td>
<td></td>
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</tbody>
</table>

Figure 3. Observed mean (points) and predicted (lines) plasma concentration-time profiles for 5 mg rosuvastatin p.o. dose administered after 600 mg 30 min i.v. infusion of rifampicin (A) and 600 mg p.o. dose of rifampicin (B). Experimental data were obtained from literature [10]. Bars represent SD.

CONCLUSIONS
➢ This study demonstrates the utility of PBPK modeling to explore the mechanisms of drug disposition and pharmacokinetics.
➢ The absorption and pharmacokinetics of rosuvastatin were accurately captured by the model which included only key transporters. The model successfully predicted DDIs related to the inhibition by rifampicin of multiple transporters involved in disposition of rosuvastatin.
➢ This model can be extended for quantitative prediction of the impact of genetic polymorphisms and DDIs mediated by OATP 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
2. Lukacova et al. Poster presentation, In APSF Annual Meeting, Atlanta, GA; 2009.