A Dynamic Physiologically-Based Pharmacokinetic (PBPK) Model to Predict the Disposition of Rosuvastatin in Human and the Extent of Drug-Drug Interactions

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Background

The FDA have proposed using rosuvastatin as a probe substrate to investigate transport-mediated drug-drug interactions (tDDIs) [1]. Indeed, 7.1-fold and 10.6-fold increases in AUC and Cmax, respectively, were reported for rosuvastatin, after co-administration of Cyclosporine A (CsA) in non-matched populations (heart transplant recipients undergoing multiple drug therapy versus healthy volunteers (HV)) [2].

Objective

To predict the tDDI between rosuvastatin and CsA in a (HV) population using mechanistic and dynamic physiologically-based pharmacokinetic (PBPK) modelling.

Methods

Relevant in vitro and in vivo data for rosuvastatin and CsA were obtained from the literature and incorporated into the permeability-limited intestinal (ADAM) and liver models within the PBPK module of the Simcyp Simulator (Version 12) (Figures 1a-c). The liver is divided into three compartments: extracellular water (EW), intracellular water (IW) and capillary blood, and the distribution between the compartments is dynamic as described in Figure 1c. Specifically, active and passive intestinal efflux (BCRP) and kinetic transport data accounting for the hepatic sinusoidal uptake (OATP1B1, OATP1B3, OATP2B1 and NTCP) and canalicular efflux of BCRP were incorporated into the PBPK model (Table 1). The passive diffusion clearance (CLP(D)) was obtained from human hepatocyte uptake studies. The Simcyp Parameter Estimation (PE) module was used to estimate a global hepatic active uptake (CLP(E)) value and this was apportioned to the individual transporters based on the % contribution of each to the hepatic uptake in vivo. The canalicular efflux clearance of BCRP was assigned based on Sandwich culture data.

The rosuvastatin model was validated against observed data and then used for prediction of the IDDI with CsA, an inhibitor of OATP1B1, OATP1B3, OATP2B1, NTCP and BCRP (Table 2).

Results

Simulations of rosuvastatin PK profiles

Simulated rosuvastatin plasma concentration-time profiles following oral doses (10 - 80 mg) were reasonably consistent with observed data from 10 independent clinical studies in HV (Figure 2).

Simulations of IDDI for Rosuvastatin

When rosuvastatin (10 mg, OD, MD) was co-administered with CsA (200 mg, BID) during 10 days in HV, predicted median AUC and Cmax ratios for 10 virtual trials ranged from 1.55 to 1.73 and 3.18 to 3.91, respectively (Figure 3).

Conclusions

Although the predicted increase in exposure of rosuvastatin following co-administration of CsA is lower than observed in vivo, it should be noted that the latter study was performed in heart transplant recipients undergoing multiple drug therapy. Nevertheless, the PBPK model presented here for rosuvastatin is able to recover in vivo concentration-time profiles and is sensitive to inhibition of the transporters OATP1B1, OATP1B3, OATP2B1, NTCP and BCRP. Thus, mechanistic PBPK modelling used in conjunction with in vitro and in vivo data can be used to investigate the complex interplay of multiple proteins for rosuvastatin, resulting in estimations of its disposition and potential DDIs.

Table 1 - Input data for the hepatic transport.

<table>
<thead>
<tr>
<th>Contribution (%)</th>
<th>CL Value (μL/min/10^6 cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLP(D) (liver)</td>
<td>2.5</td>
</tr>
<tr>
<td>Sinusoidal Uptake:</td>
<td></td>
</tr>
<tr>
<td>Global CLP(U)</td>
<td>100</td>
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<tr>
<td>OATP1B1</td>
<td>49</td>
</tr>
<tr>
<td>OATP1B3</td>
<td>16</td>
</tr>
<tr>
<td>OATP2B1/NTCP</td>
<td>35</td>
</tr>
<tr>
<td>Canalicular Efflux (BCRP)</td>
<td>- 1.23</td>
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</tbody>
</table>

Table 2 - Transporter inhibition data.

<table>
<thead>
<tr>
<th>Transporter</th>
<th>CsA K, [μM]</th>
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<tbody>
<tr>
<td>OATP1B1</td>
<td>0.014 [3]</td>
</tr>
<tr>
<td>OATP1B3</td>
<td>0.007*</td>
</tr>
<tr>
<td>BCRP</td>
<td>0.28*</td>
</tr>
<tr>
<td>OATP2B1/NTCP</td>
<td>0.07 [5]</td>
</tr>
</tbody>
</table>

Abbreviations

AUC: Area under the concentration-time curve; BCRP: Breast cancer resistance protein; CsA: Cyclosporine A; NTCP: Sodium-taurocholate co-transporting polypeptide; OATP: Organic anion-transporting polypeptides;

References

[3] Amundsen et al., Drug Metab. Disip. 2010; 38, p1499
[5] He et al., Gastroenterology 2006; 130, p1793
[14] Pasanen et al., Clin. Ther. 2007; 29, p726