Application of mechanistic PBPK modelling to evaluate the power of pharmacogenomics studies using OATP1B1 and rosuvastatin as an example

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METHODS

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• HMG-CoA reductase inhibitors (statins) are one of the most important drug classes used worldwide in the treatment of hypercholesterolemia.
• Several drug transporters have been implicated in the intestinal absorption and hepatobiliary clearance of hydrophilic statins, such as pravastatin and rosuvastatin.
• Recent research has identified key single-nucleotide polymorphisms (SNPs) in the genes encoding these drug transporters.
• In particular, several SNPs in the coding sequence of SLCO1B1 (including c.521T>C and c.388A>G) have been associated with variable activity of this solute carrier (SLC) in vitro.
• These observations have led to a rise in clinical studies comparing the effect of these polymorphisms on the pharmacokinetics (PK) and –dynamics (PD) of statins.

The aim of this study was to evaluate the influence of sample size on the ability to detect an effect of OATP1B1 phenotype on rosuvastatin pharmacokinetics using physiologically-based pharmacokinetic (PBPK) modelling.

OATP1B1-OATP1B3 Co-linearity

A link between the expression of these two transporters was established by combining the CLint value for OATP1B1 (36 µL/min/million cells) with the value assigned to OATP1B3 (109 µL/min/million cells), resulting in a final combined CLint for OATPs of 145 µL/min/million cells.

Rosuvastatin MechKiM

A CLint of 9.84 x 10-2 mL/min/million PTCs was derived from Caco-2 permeability data1,2, scaled via total nephron surface area, kidney weight and PTCs/gm kidney. Using this CLint value and accounting for glomerular filtration, CLint was predicted. Assuming a constant CLint and renal metabolism, active transport CLint via OAT3 and BCRP was calculated to be 1100 µL/min/million cells, assuming equal unidirectional transport across both membranes.

Table 1 – OATP phenotypes compared in this study and diplotypes associated with each phenotype definition. Relative abundance and relevant population variability for each phenotype was included for each test population.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Diplotype</th>
<th>Relative Abundance</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET</td>
<td>*1a/*1b, *1a/*14, *1a/*1a, *1b/*1a, *1a/*35</td>
<td>1</td>
<td>74%</td>
</tr>
<tr>
<td>IT</td>
<td>*1a/*5, *1b/*15, *1a/*15, *5/*14, *14/*15</td>
<td>0.68</td>
<td>54%</td>
</tr>
<tr>
<td>PT</td>
<td>*5/*5, *15/*15, *5/*15</td>
<td>0.37</td>
<td>35%</td>
</tr>
</tbody>
</table>

OATP extensive transporter (ET), intermediate transporter (IT) and poor transporter (PT) phenotype populations were created, where each phenotype was assigned based on a combination of haplotypes involving c.521T>C, c.388A>G, c.463C>A and c.1929A>C (Table 1). Relative abundance and the related population variability of each phenotype was obtained from meta-analysis of published studies and included as a systems-parameter in the simulations.

Simulations were performed in 160 Caucasian healthy volunteers (HVs) with the different OATP phenotypes following 10- mg single-dose oral administration to assess the pharmacokinetic parameters compared to observed data.

RESULTS

Power analysis was carried out to determine the sample size required to detect a significant difference in rosuvastatin AUC0-4hr (ng/mL) with at least 80% power:
• Subjects were assumed to have been genotyped prior to study start
• A maximum of 500 subjects/phenotype group was compared
• BCRP phenotype was kept constant between the test groups

CONCLUSION

The current study represents the first in which PBPK modelling in conjunction with a power calculation algorithm has been used to investigate the influence of OATP1B1 polymorphisms on sample size in clinical studies.

This study highlights the importance of co-linearity in expression between transporter genes on inter-individual variability, which can result in lower subject numbers required to achieve the same power.

We are currently investigating the role of BCRP polymorphisms, in addition to the influence of a potential OATP1B1-BCRP co-linearity on study power.

REFERENCES