Poster M1016

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

Ariane Emami Riedmaier, Howard Burt, Khaled Abduljalil and Sibylle Neuhoff

Simcyp (A Certara Company), Sheffield, UK. Ariane.EmamiRiedmaier@certara.com

BACKGROUND AND PURPOSE

- 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.

METHODS

The full PBPK model for rosuvastatin available within the Simcyp Simulator (v.14)[1,2] was updated with relevant population-specific data to account for the reported OATP1B1 and OATP1B3 co-linearity[3]. The model was also extended to include a permeability limited kidney model (MechKiM) and required drug-specific data to account for the involvement of renal transporters OAT3 (*SLC22A7*) and BCRP (*ABCG2*) in the uptake and efflux of rosuvastatin, respectively (Figure 1).

OATP1B1-OATP1B3 Co-linearity

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

Rosuvastatin MechKiM

A CL_{PD} of 9.84 x 10^{-2} mL/min/million PTCs was derived from Caco-2 permeability data[1,4], scaled via total nephron surface area, kidney weight and PTCs/gram kidney. Using this CL_{PD} value and accounting for glomerular filtration, CL_R was predicted. Assuming a constant CL_{PD} and renal metabolism, active transport $CL_{int,T}$ 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.

Phenotype	Diplotype	Relative Abundance	CV
ET	*1a/*1b, *1a/*14, *1a/*1a, *1b/*1a, *1a/*35	1	74%
IT	*1a/*5, *1b/*15, *1a/*15, *5/*14, *14/*15	0.68	54%
PT	*5/*5, *15/*15, *5/*15	0.37	35%

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.

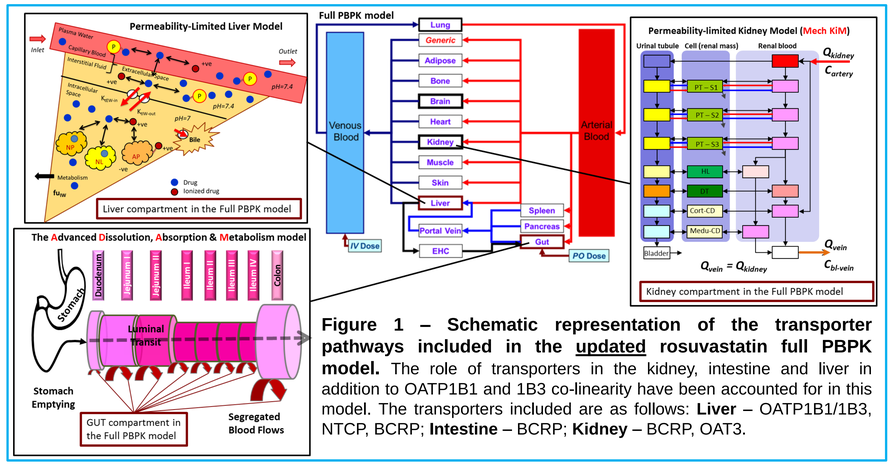

Figure 1 – Schematic representation of the transporter pathways included in the updated rosuvastatin full PBPK model. The role of transporters in the kidney, intestine and liver in addition to OATP1B1 and 1B3 co-linearity have been accounted for in this model. The transporters included are as follows: **Liver** – OATP1B1/1B3, NTCP, BCRP; **Intestine** – BCRP; **Kidney** – BCRP, OAT3.

Power analysis was carried out to determine the sample size required to detect a significant difference in rosuvastatin $AUC_{0\text{-}48hr}$ (ng/mL.h) 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

RESULTS

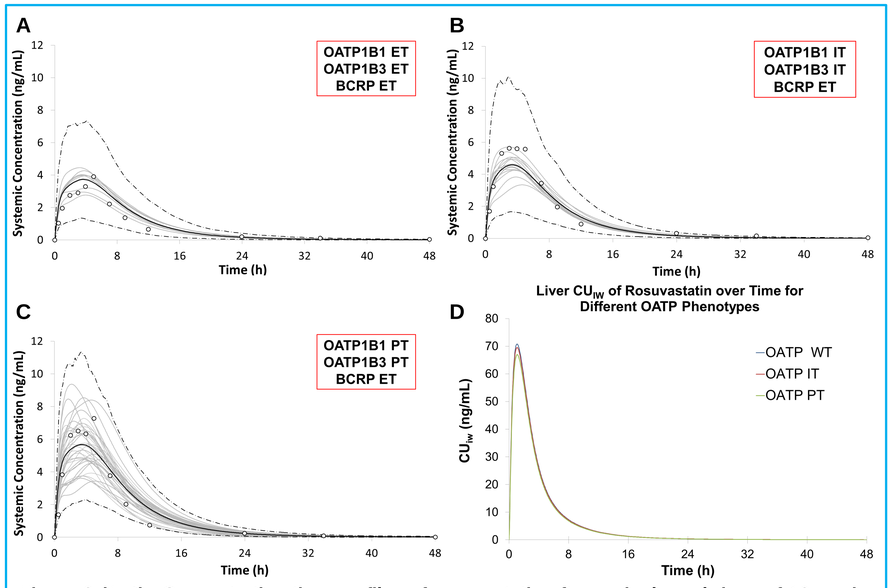

Figure 2 (A-D)– Concentration-time profiles of rosuvastatin after a single oral dose of 10 mg in HVs with different OATP phenotypes, while keeping BCRP phenotype constant. (A-C) Simulated and observed concentration-time profiles. Simulations were performed in 160 total subjects in every group, matched to the observed study design (Pasanen *et al.* 2007) regarding gender, age and subject number. Empty circles represent observed mean values from the reference study by Pasanen *et al.*[5] Solid black lines represent the simulated trials and the grey dotted lines represent the 5th and 95th percentile. (D) Simulated influence of OATP phenotype on hepatic unbound intracellular water concentrations of rosuvastatin, which is the relevant driving concentration for the PD model.

The simulated profiles of rosuvastatin for different OATP phenotypes were in agreement with previously reported clinical values[5]. Additionally, OATP phenotype did not influence the PD response to rosuvastatin in this **extended** model[2].

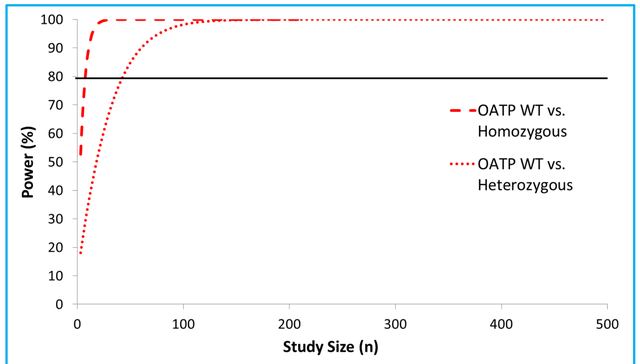

Figure 3 – Power of detecting differences in rosuvastatin AUC in the presence of OATP polymorphisms. These power analyses indicated that 8 PT and 45 IT subjects will be required to achieve 80% power to discriminate the $AUC_{0\text{-}48hr}$ of rosuvastatin from extensive transporter phenotype carriers. BCRP phenotype was not found to affect the study power.

- Given the low frequency (<3%) of the homozygous variants in the Caucasian population, post-hoc analyses will limit the robustness of studies involving OATP polymorphism, as has been observed previously in several clinical studies[6,7].
- Basing the power analysis on variability in the pharmacokinetic parameters, instead of population variability (used in this study) resulted in a lower number of subjects/group needed to achieve 80% study power – emphasizing the importance of correctly accounting for inter-individual variability in the transporter abundance data when doing power analyses.

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

1. Jamei *et al.* 2014. *Clin Pharm*. 53: 73-87.
2. Rose *et al.* 2014. *CPT Pharmacometrics Syst. Pharmacol.* 3: 1-9.
3. Nies *et al.* 2013. *Genome Medicine.* 5 (1):1-11.
4. Li *et al.* 2011. *Drug Metab Dispos*. 39(7):1196–202.
5. Pasanen *et al.* 2007. *Clin Pharmacol Ther.* 82 (6): 726-733.
6. Lee *et al.* 2005. *Clin Pharmacol Ther.* 78(4): 330-341.
7. Birmingham *et al.* 2015. *Eur J Clin Pharmacol.* 71: 329-340.