Application of a Physiologically Based Pharmacokinetic/Pharmacodynamic (PBPK/PD) Model to Investigate the Effect of OATP1B1 Genotypes on the Cholesterol Synthesis Inhibitory Effect of Rosuvastatin

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Background

Polymorphisms in the organic anion transporting polypeptide1B1 (OATP1B1) have been implicated in altered drug disposition and clearance of a number of drugs including statins. In particular, the c.521T>C single nucleotide polymorphism (SNP), which leads to a Val174Ala change, present at an allele frequency of 14% in Caucasians, 11-16% in Japanese and 2% in African Americans [1,2] has been associated with reduced hepatic uptake and increased plasma concentrations of a number of statins, including rosuvastatin (reviewed in [3]).

Hepatocytes are not only a site of clearance of statins, including rosuvastatin, but are also the site of action of statins since their target, HMG-CoA reductase, is predominately localised within hepatocytes. Therefore, altered hepatic disposition may contribute to variability in the pharmacodynamics (PD) response in addition to variability in the pharmacokinetic (PK) profile.

Objectives

To develop a PBPK/PD model that links the hepato-cellular concentrations of rosuvastatin, predicted by a permeability-limited liver model within a whole body PBPK model, to the rate of cholesterol synthesis over time and to use the model to estimate the impact of OATP1B1 c.521TT, TC and CC sequence variations on the response.

Methods

A PBPK/PD model of rosuvastatin in the Healthy Volunteer (HV) population was constructed in the Simcyp Simulator v12.2 (Figure 1).

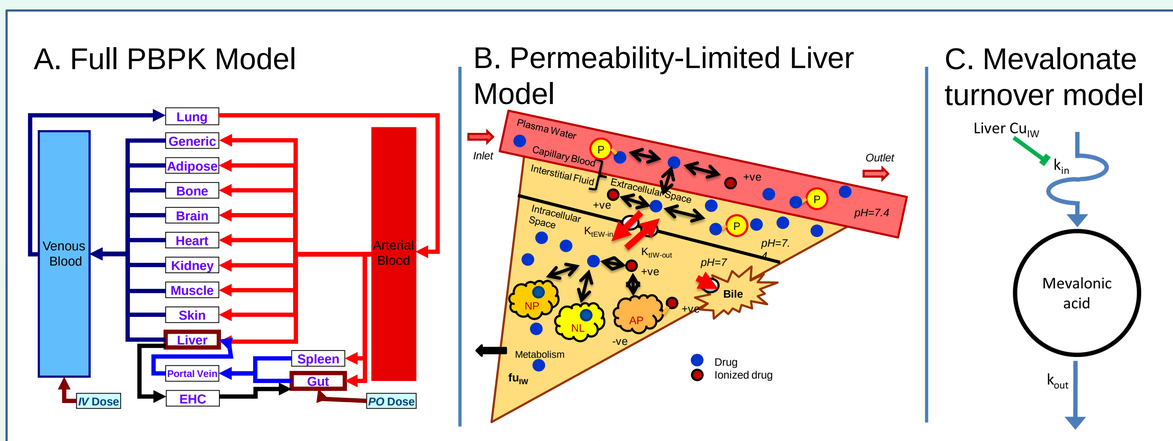

Figure 1. The whole body PBPK model (A) and permeability-limited liver model (B) within Simcyp V12.2 were used to model the plasma and Cu_{IW} for rosuvastatin. (C) Mevalonic acid turnover model; an indirect response model modified with circadian rhythm on the input rate (k_{in}) used as the PD response model (adapted from [4]).

Using clinically observed concentration-time data, the Simcyp Parameter Estimation module (using the Nelder Mead optimization algorithm) was employed to obtain the uptake clearance of rosuvastatin into the liver for OATP1B1 genotypes with c.521TT, TC and CC sequence variations [5].

The structural model for the effect of rosuvastatin on cholesterol synthesis was coded using the custom PD scripting facility within the Simcyp Simulator and was based on the report by Aoyama *et al*., (2010) [4]. The parameters for baseline were kept as in the original publication. However, the drug effect (inhibition of mevalonic acid synthesis) in our model was driven by the unbound intracellular water concentration (Cu_{IW}) in liver (as opposed to plasma). Therefore, associated values (IC_{50} and the Hill coefficient for the inhibitory sigmoid E_{max} function) were obtained by re-fitting the data (using the maximum likelihood optimization algorithm) in the Caucasian population (dominantly wild-type OATP1B1 genotype).

Simulations were performed to predict the PD response for the three OATP1B1 genotype groups in the HV population. Simulations were run as 10 trials of 10 healthy volunteers, age 20-50 and 50% female dosed with 10mg oral rosuvastatin, either single dose (plasma and liver Cu_{IW} $AUC_{0\text{-}48h}$) or at 18:00 daily for 5 days (mevalonic acid AUC, results are for the final dose).

Results

1. Parameter Estimation

Parameter estimates for OATP1B1 hepatic uptake clearance (CL_{int}) were 126, 30.2 and 0 µL/min/10^{-6} cells for the c.521TT, TC and CC genotypes, respectively. Estimated IC_{50} and Hill coefficient for the drug effect based on rosuvastatin liver Cu_{IW} were 0.12µM and 1.1, respectively. The final model incorporating estimated parameters allowed adequate recovery of PK and PD profiles (Figures 1 and 2, respectively).

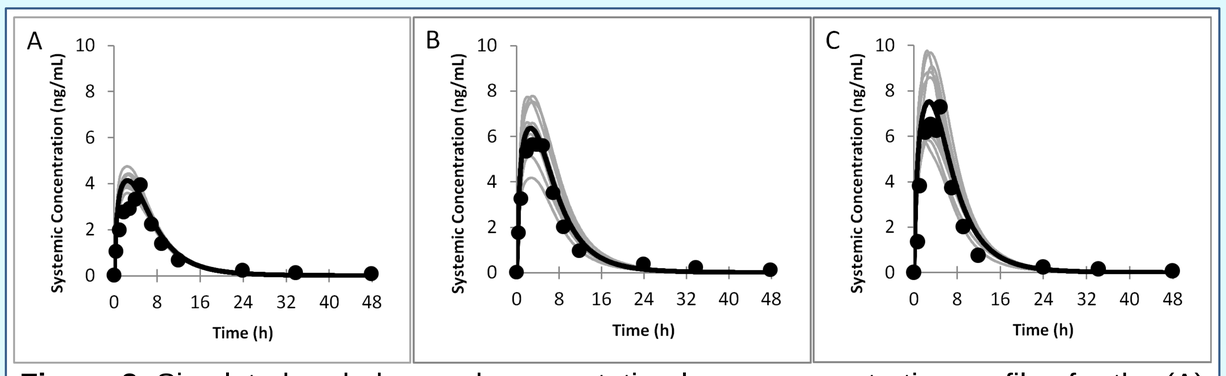

Figure 2. Simulated and observed rosuvastatin plasma concentration profiles for the (A) wild type (c.521TT) (B) heterozygous and (C) homozygous deficient (c.521CC) OATP1B1 sequence variations. Grey lines represent the mean of 10 simulated trials and the solid black lines the mean of the simulated population (c.521TT 160 subjects; c.521TC 120 subjects; c.521CC 40 subjects). Filled circles represent data extracted from Pasanen *et al.,* (2007) [5]. Simulated trial size, proportion of females and age were matched to that reported in [5] for each genotype group.

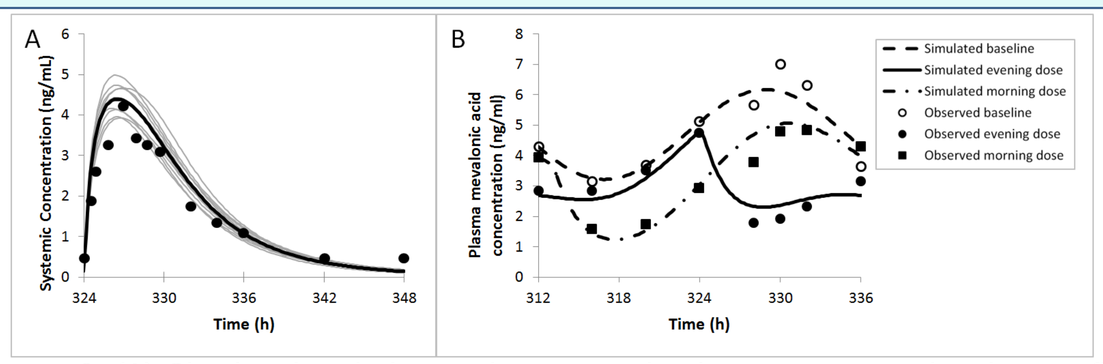

Figure 3. (A) Simulated and observed rosuvastatin plasma concentration-time profile after multiple once daily dosing of 10 mg for 14 days. Grey lines represent the mean of 10 simulated trials of 10 individuals, the solid black lines the mean of the simulated population and filled circles are data extracted from Aoyama *et al.,* (2010) [4]. (B) Mean simulated (lines) and observed (markers; from [4]) plasma mevalonic acid-time profile before rosuvastatin administration (baseline) and after evening (18:00) or morning (07:00) administration of rosuvastatin. The time is 06:00 at 312h. Simulated trial size, proportion of females and age were matched to that reported in [4].

2. Predicted impact of OATP1B1 sequence variations on PD response

Simulations showed that while the mean plasma $AUC_{0\text{-}48h}$ was increased by 57% and 102% for the heterozygote and homozygote relative to the wild type, the liver Cu_{IW} AUC was reduced by 6.2% and 9.2%, respectively (Table 1). The corresponding mevalonic acid AUC relative to baseline was reduced by 2.8% and 5.2%, respectively (Table 1).

Table 1. Mean simulated plasma $AUC_{0\text{-}48h}$, liver Cu_{IW} $AUC_{0\text{-}48h}$ and mevalonic acid AUC relative to baseline for the three OATP1B1 genotypes investigated.

OATP1B1 genotype	Plasma $AUC_{0\text{-}48h}$ (ng/ml.h)	Liver Cu_{IW} $AUC_{0\text{-}48h}$ (ng/ml.h)	Mevalonic 24h AUC relative to baseline (%)
c.521**TT**	36.4	120	38.3
c.521**TC**	57.2	112	37.2
c.521**CC**	73.7	109	36.3

Conclusions

While some studies have indicated an association between the OATP1B1 c.521T>C sequence variations and reduced therapeutic response to statins, others have failed to support this [3]. The PBPK/PD modeling approach used in this study suggests only a small contribution of the c.521T>C single nucleotide polymorphism to the interindividual variability in cholesterol synthesis effect of rosuvastatin. Compared to plasma concentration, linking the PD response to the concentration at the site of action predicted by a whole body PBPK model combined with a permeability-limited liver model allowed better insight into the impact of transporter genotype on PD response.

Although this study focused on predicting the impact of a single OATP1B1 SNP, it could be extended to predict the contribution of other genetic variants of OATP1B1 as well as other hepatic uptake or efflux and gut efflux transporters (e.g. breast cancer resistance protein (BCRP)) on rosuvastatin PK and PD, and combine to explain ethnic differences in response [2]. Such an extension would be facilitated by availability of absolute abundance and transport activity data for transporters by genotype that can be scaled by *in vitro-in vivo extrapolation* (IVIVE) approaches, but these data are currently lacking.

Models which mechanistically account for local PK variability, as presented here, improve understanding of the apparent observed PD variability and help in dissecting out the true system mediated variations in response [6].

References

[1] Tirona (2001) J Biol Chem 38: 35669-35675; [2] Niemi et al. (2011) Pharm Rev 63: 157-181; [3] Pasanen et al. (2007) Clin Pharmacol Ther 82: 726-733; [4] Tomita et al. (2013) Clin Pharmacol Ther. Advance online publication. doi: 10.1038/clpt.2012.221; [5] Aoyama et al. (2010) Biol Pharm Bull 33: 1082-1087; [6] Rostami-Hodjegan (2013) Clin Pharmacol Ther 93: 152