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 transporter-mediated drug-drug interactions (tDDIs) [1]. Indeed, 7.1-fold and 10.6-fold increases in AUC and $C_{max,}$ 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

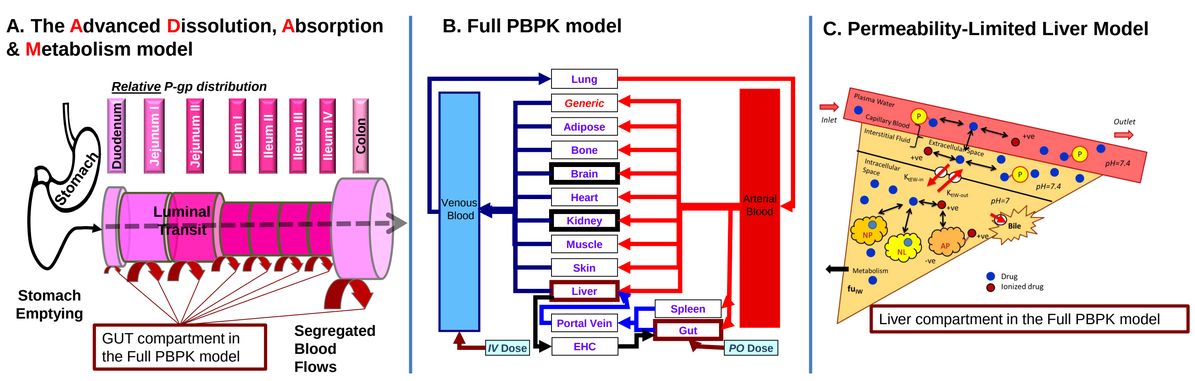

Figure 1 *- The Full-PBPK model within Simcyp V12.1 and the two permeability-limited models, for gut and liver. These models have been used for the substrate, Rosuvastatin, and the first inhibitor, CsA. Left: The permeability –limited gut model, ADAM; Right: The permeability-limited liver model, PerL.*

intestinal efflux (BCRP) and kinetic transport data accounting for the hepatic sinusoidal uptake (OATP1B1, OATP1B3, OATP2B1 and NTCP) and canalicular efflux (BCRP) of rosuvastatin were incorporated into the PBPK model (Table 1). The passive diffusion clearance (CL_{PD}) was obtained from human hepatocyte uptake studies. The Simcyp Parameter Estimation (PE) module was used to estimate a global hepatic active uptake ($CL_{int,T}$) value and this was apportioned to the individual transporters based on the % contribution of each to the hepatic uptake *in vitro.* The canalicular efflux clearance of BCRP was assigned based on Sandwich culture data.

Table 1 - Input data for the hepatic transport.

	Contribution (%)	CL Value [µL/min/10^6 cells]
CL_{PD} (liver)	-	**2.5**
Sinusoidal Uptake:		
Global CL_{int}	100	222
OATP1B1	49	**109**
OATP1B3	16	**36**
OATP2B1 / NTCP	35	**78**
Canalicular Efflux (BCRP)	-	**1.23**

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

Table 2 - Transporter inhibition data. *****Estimated by applying correction factors to the OATP1B1 CsA K_i to obtain similar relative inhibitory potencies to Clarke *et al*., 2011 [4].

Transporter	CsA K_i [µM]
OATP1B1	0.014 [3]
OATP1B3	0.007*
BCRP	0.28*
OATP2B1 / NTCP	0.07 [5]

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;

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).

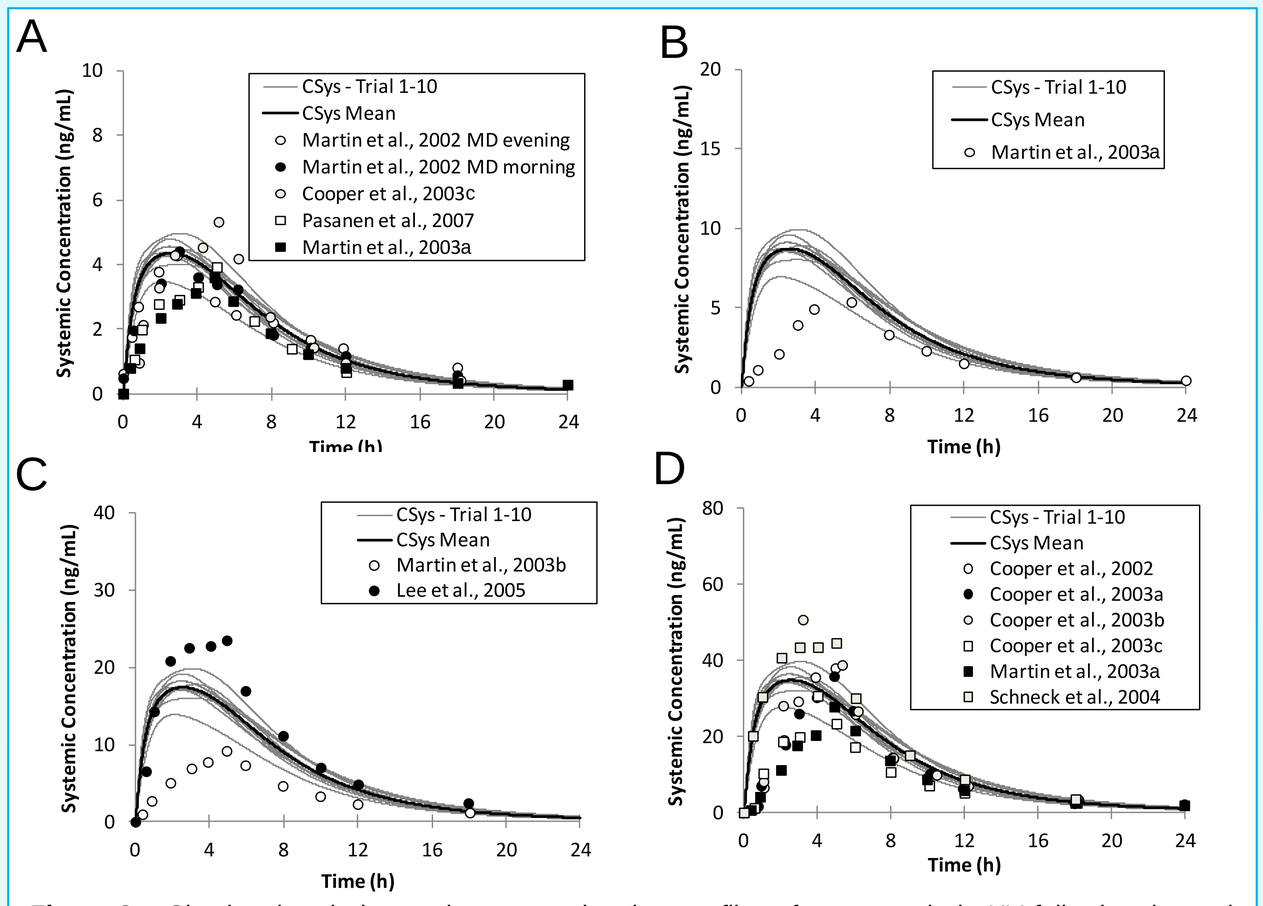

Figure 2 – *Simulated and observed concentration-time profiles of rosuvastatin in HV following the oral administration of (A) 10, (B) 20, (C) 40 and (D) 80 mg, respectively. The grey lines represent simulated individual trials (10 x 10) and the solid black lines are the simulated mean of the HV population (n=100). The circles denotes mean observed values from clinical studies [6–15].*

Simulations of tDDI for Rosuvastatin

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

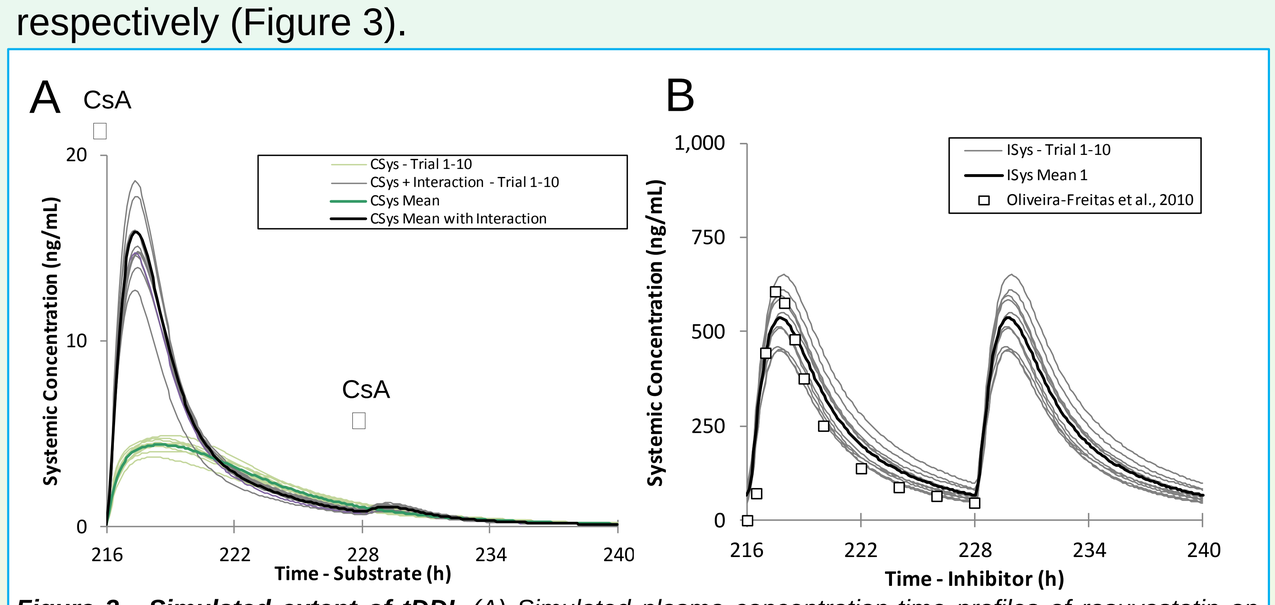

Figure 3 - Simulated extent of tDDI. *(A) Simulated plasma concentration-time profiles of rosuvastatin on day 10 (10 mg, MD) in 10 virtual trials of 10 HV without interaction of CsA (green lines) and with interaction of CsA (200 mg, BID) (black lines). (B) Simulated plasma concentration-time profiles of the inhibitor, CsA. Overlay data are from Oliveira-Freitas et al., 2010 [16].*

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.

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