Physiologically Based Pharmacokinetic Modeling of Rosuvastatin and Prediction of Transporter-Mediated Drug-Drug Interactions Involving Rifampicin

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PURPOSE

Statins have been extensively used worldwide for the treatment of cardiovascular diseases. However, compliance which is a key for the best treatment outcomes is the issue due to the side effects. Understanding the underlying mechanisms involved in the disposition of statins is required for optimal dosing to improve compliance.

PBPK modeling approach allows to investigate and identify the underlying mechanisms to better understand ADME processes and determinants of drug interactions. Rosuvastatin (Crestor®) is a commonly prescribed lipid-lowering agent from the statins class for the treatment of primary hyperlipidemia and hypertriglyceridemia. Rosuvastatin is a substrate for multiple transporters including organic anion transporting polypeptides (OATP1B1 and OATP1B3), sodium-taurocholate cotransporting polypeptide (NTCP), breast cancer resistance protein (BCRP), and exhibits minor metabolic clearance. The objective of this study was to develop a physiologically based pharmacokinetic (PBPK) model of rosuvastatin and to apply this model to predict the transporter-mediated drug-drug interactions (DDIs) with rifampicin, which is an inhibitor of multiple drug transporters.

METHODS

The GastroPlus® 9.7 (Simulations Plus, Inc., Lancaster, CA) Advanced Compartmental Absorption and Transit (ACAT™) model was used in conjunction with the PBPKPlus™ and Metabolism and Transporter modules to build a mechanistic absorption/PBPK model for rosuvastatin. Physicochemical and biopharmaceutical properties that predict absorption and distribution were obtained from literature [1] or were predicted from structure with ADMET Predictor® 9.5 (Simulations Plus, Inc. Lancaster, CA). Human organ weights, volumes, and blood perfusion rates were generated by the Population Estimates for Age-Related (PEAR™) Physiology™ module.

All tissues, except the liver and kidney, were modeled as perfusion-limited tissues. Tissue/plasma partition coefficients (Kps) of perfusion- and permeability-limited tissues were calculated using the default Lukacova [2] and Poulin and Theil extracellular [3] methods, respectively. Intestinal passive absorption, BCRP-mediated efflux, and enterohepatic circulation of rosuvastatin were incorporated in the PBPK model. The permeability-limited liver model included passive and active sinusoidal uptake, metabolism, and biliary secretion mediated by active canalicular efflux. In addition, renal excretion was modeled by passive renal filtration estimated from GFR and fraction unbound in plasma (FupxGFR) and passive as well as carrier-mediated renal secretion **(Figure 1).** The possibility of involvement of OATP2B1 in uptake at gut apical, efflux by OST_α/OST_β at gut basolateral, and MRP2 efflux on basolateral side of liver was explored in the model. These transporters were not critical for the model and were dropped in the final model.

In vitro K_m values for OATP1B1, OATP1B3, NTCP, BCRP, OAT3 transporters were obtained from literature [4-6]. Due to the lack of data for MRP2, K_m of 10 µM was used. The passive diffusion was modeled using a single value of permeability-surface-area product (PStc) per cell volume (specific PStc of 0.15 mL/s/mL-cell volume) for permeability limited tissues to match ~18% of active uptake in liver estimated from *in vitro* study [1] and shape of i.v. profile. The V_{max} values for gut, liver, and kidney transporters were fitted against *in vivo* data (Cp-time profiles and urine data) after i.v. (8 mg) and single p.o. administration (40 mg) in healthy adults [7]. The metabolic clearance by major enzyme - CYP2C9 in gut and liver was modeled using GastroPlus' built-in expression levels, *in silico* K_m of 11.3 µM (ADMET Predictor® 9.5), and V_{max} fitted to obtain ~<10% elimination by metabolism [8]. Default fasted and fed physiologies were used in the model. The model was validated by comparing simulated and observed Cp-time profiles after single oral dose of 10 and 80 mg [9].

Validated rifampicin PBPK model from standard GastroPlus DDI database was used. Intestinal passive absorption and metabolic clearance by CYP3A4 in gut and liver were included in this model. Transporter-mediated DDIs between rosuvastatin and rifampicin were predicted with the GastroPlus DDI module using dynamic simulations. IC_{50} values (assumed unbound) for rifampicin inhibition of rosuvastatin for OATP1B1 (1.1 µM),1B3 (0.3 µM), NTCP (277 µM), BCRP (14 µM), and MRP2 (14.7 µM) were obtained from literature [10].

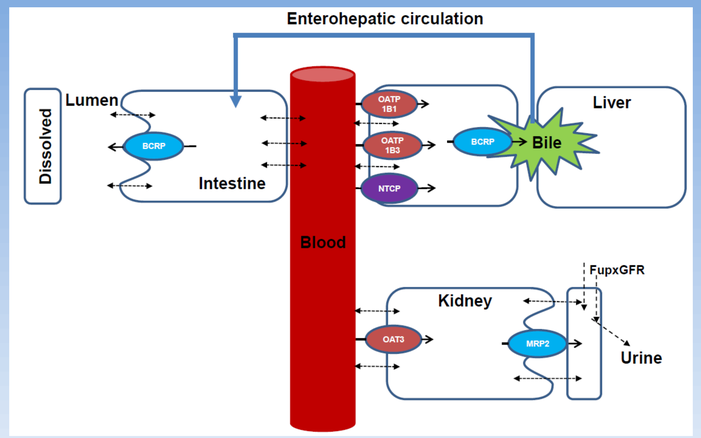

Figure 1. Overview of the major processes governing the disposition of rosuvastatin in gut, liver, and kidney.

RESULTS

- The PBPK model adequately described Cp-time profiles of rosuvastatin for a variety of doses after i.v. and p.o. administration in different populations of subjects (**Figure 2A, B, C and D**)

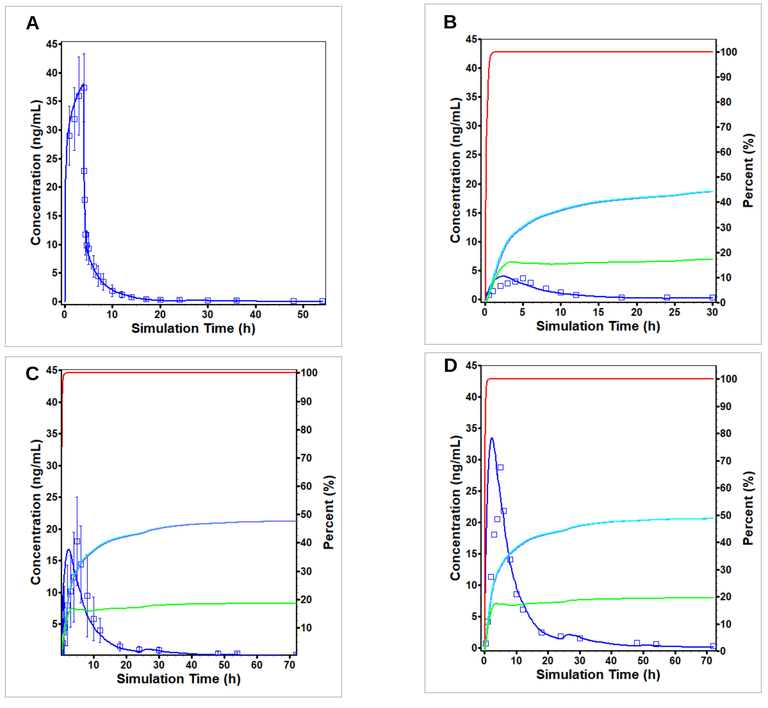

Figure 2. Observed (points) and simulated (lines) plasma concentration-time profiles of rosuvastatin after 8 mg i.v. infusion (A), single oral dose of 10 mg (B), 40 mg (C), and 80 mg (D) in healthy volunteers. Experimental data were obtained from literature [7, 9]. Cumulative amount dissolved (red), absorbed (cyan), entered portal vein (blue), and entered systemic circulation (green) are all shown on right Y-axis as percent of administered dose.

- The simulated $AUC_{0\text{-}t}$ and C_{max} values were within 0.8-1.25 of clinically observed mean data following 8 mg i.v. and 10-80 mg p.o. doses of rosuvastatin.
- The predicted DDI effect, fold increase in rosuvastatin plasma $AUC_{0\text{-}t}$ and C_{max} due to rifampicin coadministration, was within two-fold of the observed DDI effect [10] as shown in **Table 1**. The interaction is predicted very accurately for 600 mg p.o. rifampicin (~5% prediction error) but underpredicted (1.5 – 1.9-fold) with 30 min i.v. infusion of 600 mg rifampicin (**Figure 3A and 3B).**
- Magnitude of interactions was underpredicted with relative contribution of hepatic uptake transporters of rosuvastatin: ~50% OATP1B1, ~35% NTCP, and ~15% OATP1B3 estimated from *vitro* studies [11]. The interactions were better captured with reassignment of relative contribution: ~70% OATP1B1, ~10% NTCP, and ~20% OATP1B3 [12].
- Oral rifampicin inhibited intestinal efflux by BRCP which resulted in increased gut absorption. The inhibitory effect of rifampicin on MRP2 efflux transporter in kidney had no effect on rosuvastatin pharmacokinetics.

	C_{max} Ratio		$AUC_{0\text{-}t}$ Ratio	
	Observed	Predicted	Observed	Predicted
i.v. rifampicin	5.51	3.65	4.55	2.39
p.o. rifampicin	9.93	9.49	5.24	5.45

Table 1. Summary of observed and predicted DDIs of rosuvastatin with rifampicin.

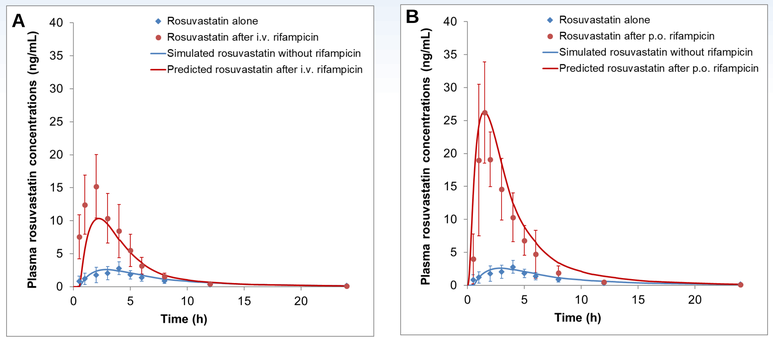

Figure 3. Observed mean (points) and predicted (lines) plasma concentration-time profiles for 5 mg rosuvastatin p.o. dose administered after 600 mg 30 min i.v. infusion of rifampicin (A) and 600 mg p.o. dose of rifampicin (B). Experimental data were obtained from literature [10]. Bars represent SD.

CONCLUSIONS

- This study demonstrates the utility of PBPK modeling to explore the mechanisms of drug disposition and pharmacokinetics.
- The absorption and pharmacokinetics of rosuvastatin were accurately captured by the model which included only key transporters. The model successfully predicted DDIs related to the inhibition by rifampicin of multiple transporters involved in disposition of rosuvastatin.
- This model can be extended for quantitative prediction of the impact of genetic polymorphisms and DDIs mediated by OATP and BCRP inhibitors.
- The model can help to identify populations at increased risk for side effects and to optimize their dosing regimens for the safe and effective use of rosuvastatin.

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