Predicting atorvastatin acid pharmacokinetics in a complex enzyme- and transporter-mediated drug–drug interaction network using physiologically based pharmacokinetic modeling

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Objectives

The aims of this work were to develop a PBPK model for atorvastatin acid, and to apply the established model to predict enzyme- and transporter-mediated DDIs involving clarithromycin, erythromycin, gemfibrozil, itraconazole, and rifampicin as perpetrator drugs.

Introduction

- Atorvastatin, an HMG-CoA reductase inhibitor, is commonly prescribed to treat dyslipidemia, a major risk factor for cardiovascular disease.[1,2]
- The recommended adult dosages ranges from 10 to 80 mg once daily. After oral intake, atorvastatin acid is quickly absorbed in the gastrointestinal tract, with peak plasma levels reached within one to two hours. Despite this, its oral bioavailability is relatively low (~ 14%) due to high first-pass metabolism by the CYP3A4 enzyme.[2]
- Atorvastatin acid is also transported by various transporters, including the influx transporters OATP1B1 and OATP1B3,[3] as well as the efflux transporters P-gp and BCRP, [4] making it prone to DDIs mediated by enzymes and transporters.

Methods

- A PBPK model of atorvastatin acid was developed using the Open Systems Pharmacology Software Suite (PK-Sim® and MoBi®, version 11.2) .[5]
- Information about physicochemical properties and absorption, distribution, metabolism, and excretion processes as well as clinical study data were gathered from the literature.
- The established model was linked with published perpetrator PBPK models of clarithromycin[6], erythromycin[7], gemfibrozil[8], itraconazole[6], and rifampicin[6].
- Here, predicted and observed AUC_{last} and C_{max} ratios were calculated evaluating the predictive DDI model performance.[9]

Results

- The developed PBPK model includes a total of 34 atorvastatin acid plasma concentration–time profiles (model building: 7 and model qualification: 27) after single and multiple oral doses across the range of 1 to 80 mg in healthy subjects.
- Metabolism via CYP3A4 and CYP3A5 (only implemented for CYP3A5 normal metabolizers) as well as transport processes via BCRP, OATP1B1/1B3, and P-gp were incorporated in the final PBPK model.
- Table 1 presents an overview of drug-dependent parameters of atorvastatin acid.
- The PBPK model was incorporated into a complex enzyme- and transporter-mediated DDI network using various perpetrator drugs (Figure 2 and 3).
- The underestimation of the erythromycin DDI and control may be attributed to DGIs that were not considered due to absence of information about enzyme and/or transporter genotypes/phenotypes (Figure 3e).
- A good DDI model performance could be demonstrated by 12/14 and 11/14 AUC_{last} and C_{max} ratios, respectively, lying within the acceptance limits proposed by Guest et al. . (Figure 4).[9]

Table 1. Drug-dependent parameters of atorvastatin acid

Parameter	Value	Source	Reference
MW (g/mol)	558.66	Literature	Zhang 2015[10]
pK_a (acid)	4.46	Literature	Zhang 2015[10]
Fraction unbound (%)	5.10	Literature	Zhang 2015[10]
Lipophilicity (log units)	4.07	Literature	Duan 2017[11]
Solubility at pH=6 (mg/ml)	1.22	Literature	Morse 2019[12]
K_m (µmol/l) BCRP/P-gp	82.41/10.70	Literature	Deng 2021[4]
k_{cat} (1/min) BCRP/P-gp	932.28/614.28	Optimized	-
OATP1B K_m (µmol/l)	0.77	Literature	Vildhede 2014[3]
OATP1B k_{cat} (1/min)	1970.16	Optimized	-
CYP3A4 K_m (µmol/l)	25.60	Literature	Jacobsen 2000[13]
CYP3A4 k_{cat} (1/min)	8.57	Optimized	-
CYP3A5 K_m (µmol/l)	42.60	Literature	Park 2008[14]
CYP3A5 k_{cat} (1/min) PM/IM/NM	0/0/1350.42	Optimized	-
Intestinal permeability (cm/s)	$4.49 \cdot 10^{-4}$	Literature	Morse 2019[11]

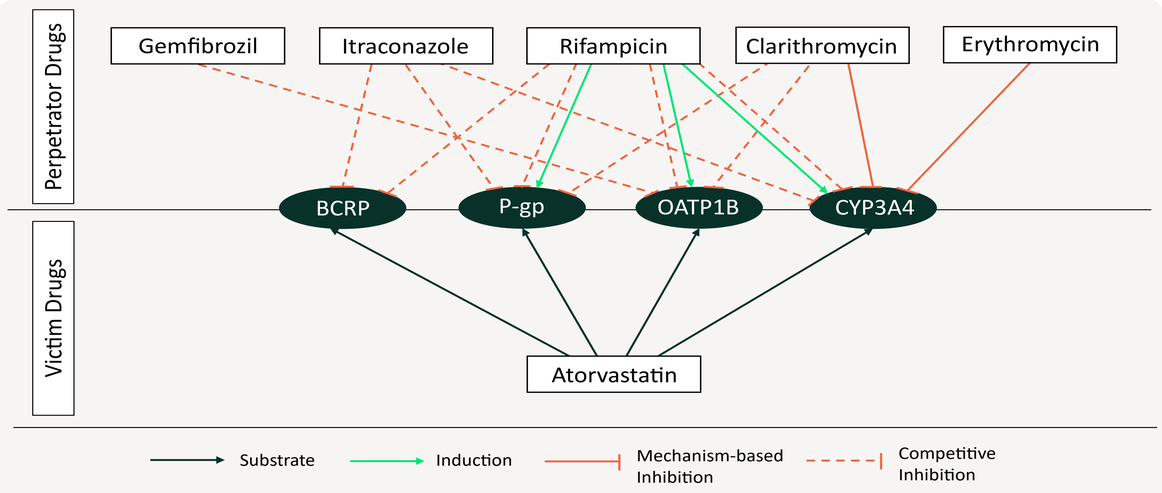

Figure 2. Overview of implemented metabolic and transport processes in the atorvastatin acid model and the DDI network.

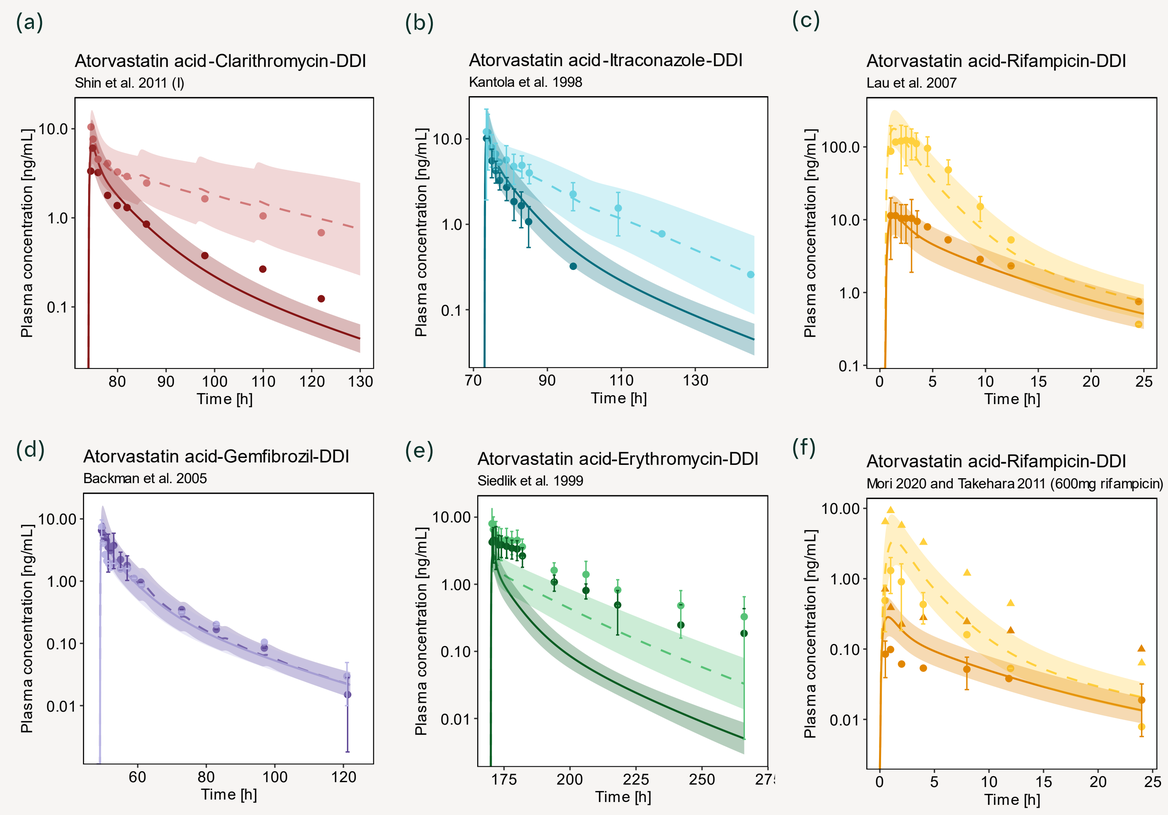

Figure 3. Predicted and observed plasma concentration–time profiles for different DDIs. Dashed and solid lines show predicted geometric mean profiles with and without intake of perpetrator drug, respectively, and ribbons the corresponding geometric standard deviation of the population simulations (n=100). Points depict mean observed atorvastatin acid concentrations with standard deviation (if available).

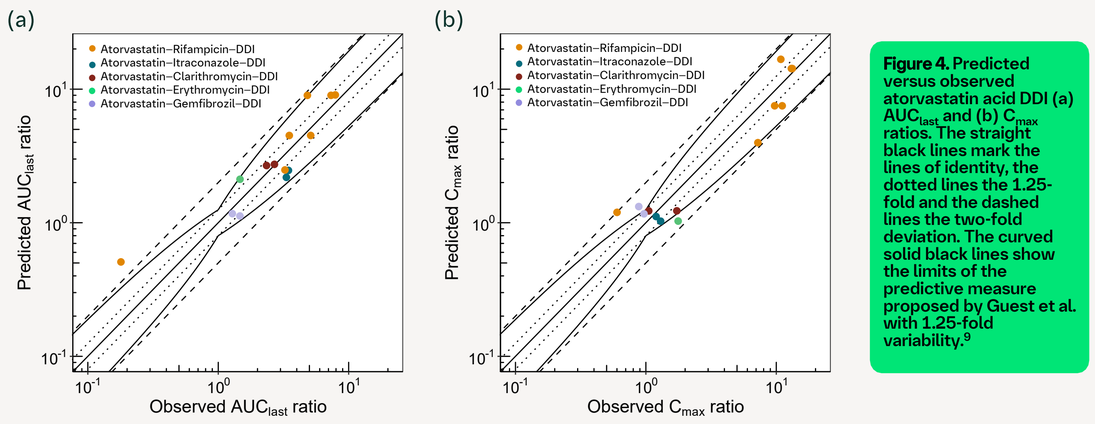

Figure 4. Predicted versus observed atorvastatin acid DDI (a) AUC_{last} and (b) C_{max} ratios. The straight black lines mark the lines of identity, the dotted lines the 1.25-fold and the dashed lines the two-fold deviation. The curved solid black lines show the limits of the predictive measure proposed by Guest et al. with 1.25-fold variability.[9]

Conclusions

A whole-body PBPK model for atorvastatin acid has been successfully developed and applied to predict various DDI scenarios.

The established PBPK model will be added to the openly accessible OSP PBPK model library and will be part of the OATP1B1/1B3 DDI OSP qualification report. It enriches the PBPK model library by an additional CYP3A4 and OATP1B1/1B3 substrate that might be leveraged for future DDI investigations.

Abbreviations

AUC_{last}, area under the plasma concentration–time curve from the first to the last time point of measurement; BCRP, breast cancer resistant protein; C_{max}, maximum plasma concentration; CYP, cytochrome P450; DDI, Drug–drug interaction; DGI, drug–gene interaction; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; IM, intermediate metabolizer; k_{cat} catalytic rate constant; K_m, Michaelis-Menten constant; MW, molecular weight; NM, normal metabolizer; OATP, organic anion transporting polypeptide; P-gp, P-glycoprotein; PBPK, Physiologically based pharmacokinetic, PM, poor metabolizer.

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