A Physiologically Based Pharmacokinetic Model of Atorvastatin Acid Predicting CYP3A4 and OATP1B Drug–Drug Interactions

Christina Kovar,[1] Tobias Kanacher,[1] Fenglei Huang,[2] Jing Wu,[2] Reinhard Sailer,[3] David Busse,[3] Jose David Gómez-Mantilla,[3] Ibrahim Ince.[3]

1. Pharmetheus AB, Sweden; 2. Boehringer Ingelheim Pharma Inc, USA; 3. Boehringer Ingelheim Pharma, Germany.

Objectives

The aims of this work were (i) to mechanistically describe the pharmacokinetics of atorvastatin acid using the compartmental whole-body PBPK model in PK-Sim®, (ii) to describe and predict enzyme- and transporter-mediated DDIs involving clarithromycin, erythromycin, gemfibrozil, itraconazole, and rifampicin as perpetrator drugs and subsequently, (iii) to provide a qualified atorvastatin acid PBPK model that might be leveraged for future DDI investigations.

Introduction

- The HMG-CoA reductase inhibitor atorvastatin is a widely prescribed statin for managing dyslipidemia, a well-established risk factor for cardiovascular disease.[1,2]
- Its recommended dosing regimen ranges from 10 to 80 mg once daily for adults.[2] Upon oral administration, atorvastatin acid is rapidly absorbed from the gastrointestinal tract achieving maximum plasma concentrations within one to two hours.[2] However, its overall bioavailability remains notably low (~14%) due to extensive first pass metabolism mediated by CYP3A4.[2]
- Additionally, atorvastatin acid is a substrate of various transporters, such as the influx transporters OATP1B1 and OATP1B3,[3] as well as the efflux transporters P-gp, BCRP, and MRP3,[4] making it susceptible to DDIs mediated by both enzymes and transporters.

Methods

- A PBPK model of atorvastatin acid has been developed using the Open Systems Pharmacology Software Suite (PK-Sim® and MoBi®, version 11.2).[5]
- Plasma profiles were divided into a training and a test dataset for model building (7 plasma concentration–time profiles) and qualification (27 plasma concentration–time profiles), respectively. To inform CYP3A4- and OATP1B1/1B3-mediated pathways, the DDI studies with itraconazole and rifampicin were allocated to the training dataset.
- The established model was linked with published PBPK models of clarithromycin[6], erythromycin[7], gemfibrozil[8], itraconazole[6], and rifampicin[6] to investigate the impact of different perpetrator drugs on the exposure of atorvastatin acid.
- Model qualification was graphically performed by comparing observed to predicted plasma concentration–time profiles as well as their respective AUC_{last} and C_{max} values.
- For DDI prediction performance, predicted and observed AUC_{last} and C_{max} ratios were calculated, and the prediction success limits proposed by Guest et al. were applied.[9] Here, a stricter criterium for DDI predictions than the traditional twofold deviation is utilized.[9]

Results

- The final PBPK model comprises metabolism via CYP3A4 as well as transport processes via OATP1B1/1B3, BCRP, MRP3, and P-gp.
- An overview of the drug-dependent parameters of atorvastatin acid, either sourced from the literature or optimized during model building, is provided in Table 1.
- Our established atorvastatin PBPK model showed a good descriptive and predictive performance, with 85% of AUC_{last} (training: 100%, test: 80%) and C_{max} values (training: 100%, test: 80%) falling within the twofold deviation (Figure 1).
- The PBPK model was incorporated into a comprehensive DDI network using a broad range of perpetrator drugs (Figure 2 and 3).
- Moreover, a good DDI performance was demonstrated by 11/14 AUC_{last} and C_{max} ratios, respectively, lying within the 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	Morse 2019[11], Zhang 2015[10]
Lipophilicity (log units)	4.07	Literature	Duan 2017[12]
Solubility at pH=6 (mg/ml)	1.22	Literature	Morse 2019[11]
K_m (µmol/l) BCRP/P-gp/MRP3	82.41/10.70/31.50	Literature	Deng 2021[4]
k_{cat} (1/min) BCRP/P-gp/MRP3	674.31/444.30/951.74	Optimized	-
OATP1B K_m (µmol/l)	0.77	Literature	Vildhede 2014[3]
OATP1B k_{cat} (1/min)	2407.55	Optimized	-
CYP3A4 K_m (µmol/l)	25.60	Literature	Jacobsen 2000[13]
CYP3A4 k_{cat} (1/min)	8.68	Optimized	-
Intestinal permeability (cm/s)	$4.49 \cdot 10^{-4}$	Literature	Morse 2019[11]

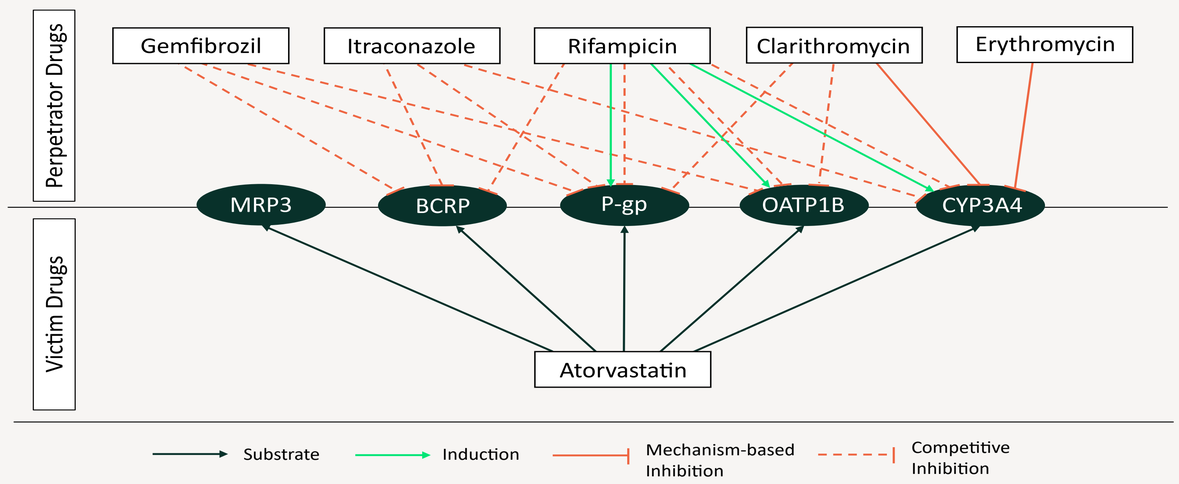

Figure 2. Overview of implemented metabolic and transport processes as well as investigated DDIs.

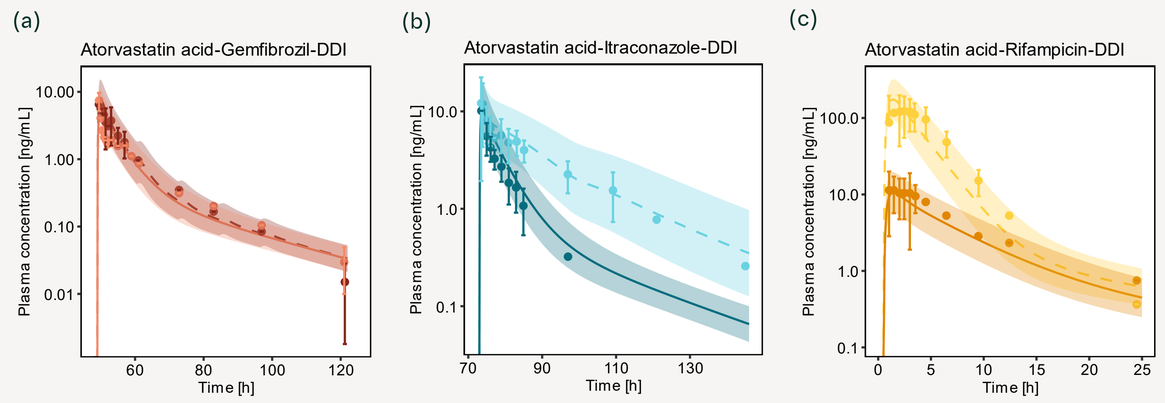

Figure 3. Predicted and observed plasma concentration–time profiles for different DDIs. Dashed and solid lines show predicted geometric mean profiles with and without intake of perpetrator drug, respectively, and ribbons the corresponding geometric standard deviation of the population simulations (n=100).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

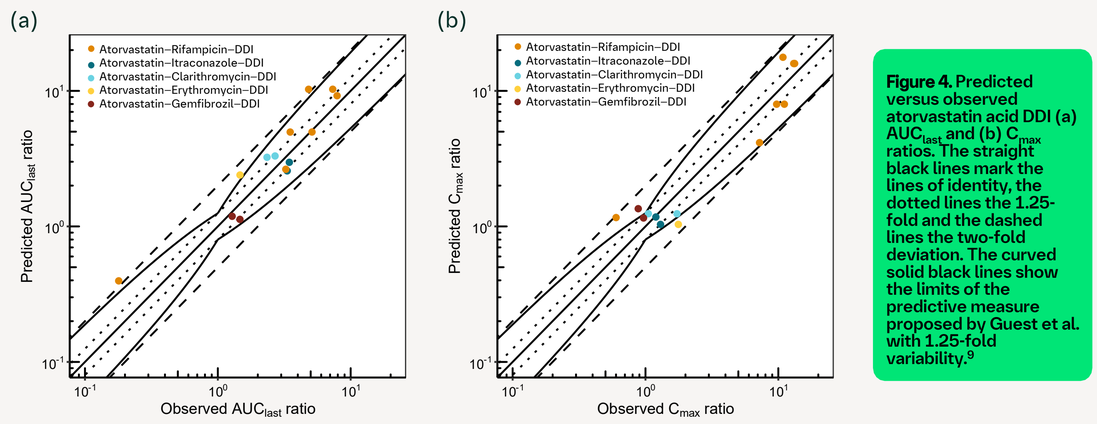

Figure 4. Predicted versus observed atorvastatin acid DDI (a) AUC_{last} and (b) C_{max} ratios. The straight black lines mark the lines of identity, the dotted lines the 1.25-fold and the dashed lines the two-fold deviation. The curved solid black lines show the limits of the predictive measure proposed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

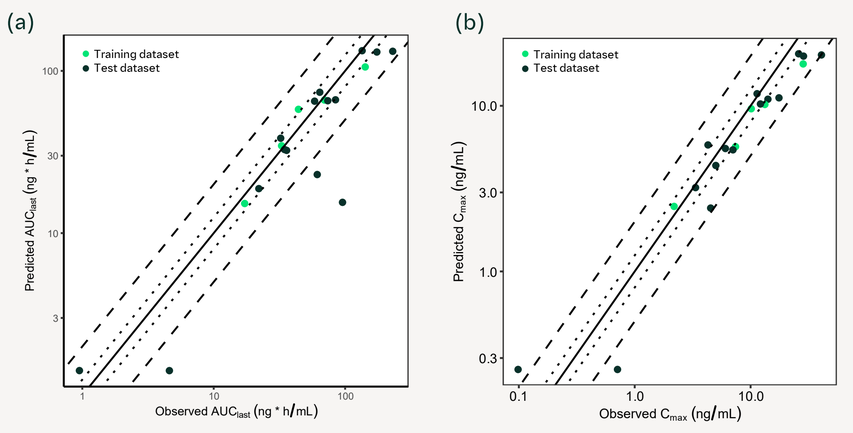

Figure 1. Predicted versus observed atorvastatin acid (a) AUC_{last} and (b) C_{max} values. Green and dark green points refer to the training and test dataset, respectively. The straight black lines mark the lines of identity, the dotted lines the 1.25-fold and the dashed lines the two-fold deviation.

Conclusions

A whole-body PBPK model for atorvastatin acid has been successfully developed, including relevant active disposition processes, and applied to describe and predict the impact of different DDI scenarios on the exposure of atorvastatin acid.

Moreover, our established PBPK model enriches the openly accessible PBPK model library by a widely used CYP3A4 and OATP1B1/1B3 substrate, which can be leveraged to predict DDI liabilities for atorvastatin acid, such as for investigational new drugs.

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; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; k_{cat} catalytic rate constant; K_m, Michaelis-Menten constant; MRP3, multidrug resistance-associated protein 3; MW, molecular weight; OATP, organic anion transporting polypeptide; P-gp, P-glycoprotein; PBPK, Physiologically based pharmacokinetic.

References

1. Ascunce RR et al. (2012), doi: 10.1007/s11883-012-0229-0
2. https://labeling.pfizer.com/ShowLabeling.aspx?id=587
3. Vildhede A et al. (2014), doi: 10.1124/dmd.113.056309
4. Deng F et al. (2021), doi: 10.1124/dmd.121.000430
5. Lippert J et al. (2019), doi: 10.1002/psp4.12473
6. Hanke N et al. (2018), doi: 10.1002/psp4.12343
7. https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/tree/master/Erythromycin
8. Türk D et al. (2019), doi: 10.1007/s40262-019-00777-x
9. Guest E J et al. (2011), doi: 10.1124/dmd.110.036103
10. Zhang T (2015), doi: 10.1016/j.ejps.2015.06.019
11. Morse BL et al. (2019), doi: 10.1002/psp4.12447
12. Duan P et al. (2017), doi: 10.1007/s13318-016-0383-9
13. Jacobsen W et al. (2000), PMID: 11038166

Pharmetheus®

Boehringer Ingelheim