



Application of Physiologically Based Pharmacokinetic Modeling and Population Pharmacokinetic Modeling to Predict Potential

Drug-Drug Interaction between Rivaroxaban and Carbamazepine

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Background and Objective

- Rivaroxaban (RIV, a direct oral anticoagulant) and carbamazepine (CBZ, an anti-epileptic drug) could be prescribed concomitantly to cerebrovascular disease patients.
- Cytochrome P450 3A4 (CYP3A4) is one of the major enzymes involved in the metabolism of RIV. Meanwhile CBZ is a strong inducer of CYP3A4. CBZ-mediated CYP3A4 induction could affect the pharmacokinetics (PK) of RIV [1]. Drug-drug interaction (DDI) between CBZ and RIV could be expected.
- However, there have been no studies investigating the potential DDI between RIV and CBZ in human. Therefore, this study was conducted to predict the potential DDI in human. The physiologically based pharmacokinetics (PBPK) and population pharmacokinetics (PopPK) model-based approaches were applied. The simulation results could provide a quantitative understanding of the CBZ effects on the RIV exposure.

Methods

• PBPK DDI modeling and simulation

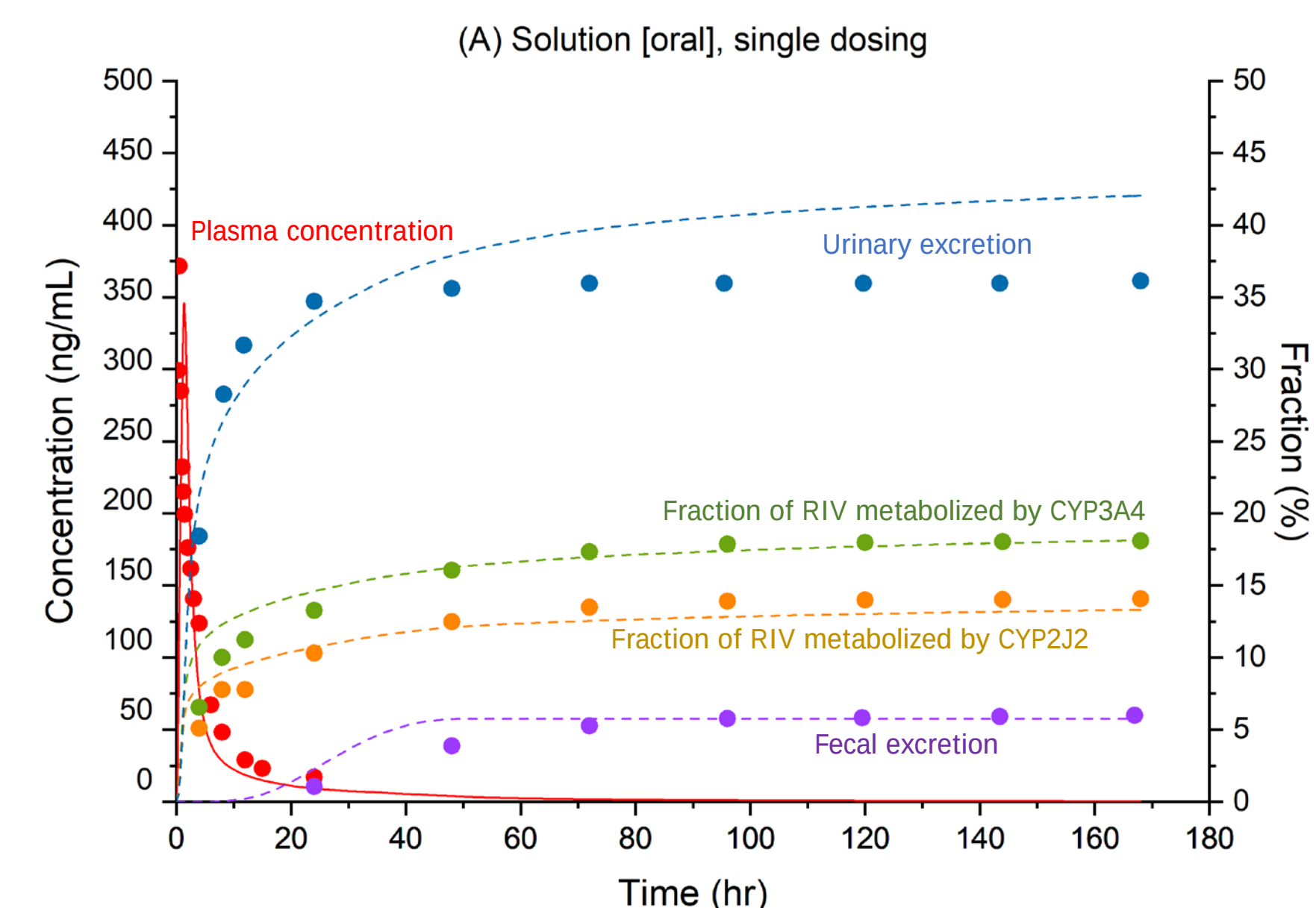
- A PBPK model for RIV was developed in PK-Sim® (Version 9.1.0) by incorporating parameters of physicochemical properties, ADME properties, and *in-vitro* metabolism related parameters that were extracted from literatures.
- The model was then verified by fitting the simulated PKs to the published clinical PKs of RIV. The clinical studies covering a broad dosing range, single- and multiple-dose studies, and different drug formulations, were selected. Plasma concentration, urinary and fecal excretion, and metabolism profiles were included.
- To predict the effect of CBZ on the PKs of RIV, the PKs of RIV with/without coadministration with CBZ was simulated and compared to each other.
- Coadministration with CBZ, the PKs of RIV was obtained by incorporating the developed RIV PBPK model with a published CBZ PBPK model verified [2].

• PopPK DDI modeling and simulation

- Our group recently published a study to investigate the effect of CBZ on the PKs of RIV in rats [3]. Therein, a PopPK model for RIV and the effect of CBZ in rats was reported.
- From the observed data and the developed PopPK model for the DDI between CBZ and RIV in rats, a simple allometric scaling and liver blood flow scaling methods were applied to extrapolate the DDI in human [3].

Results

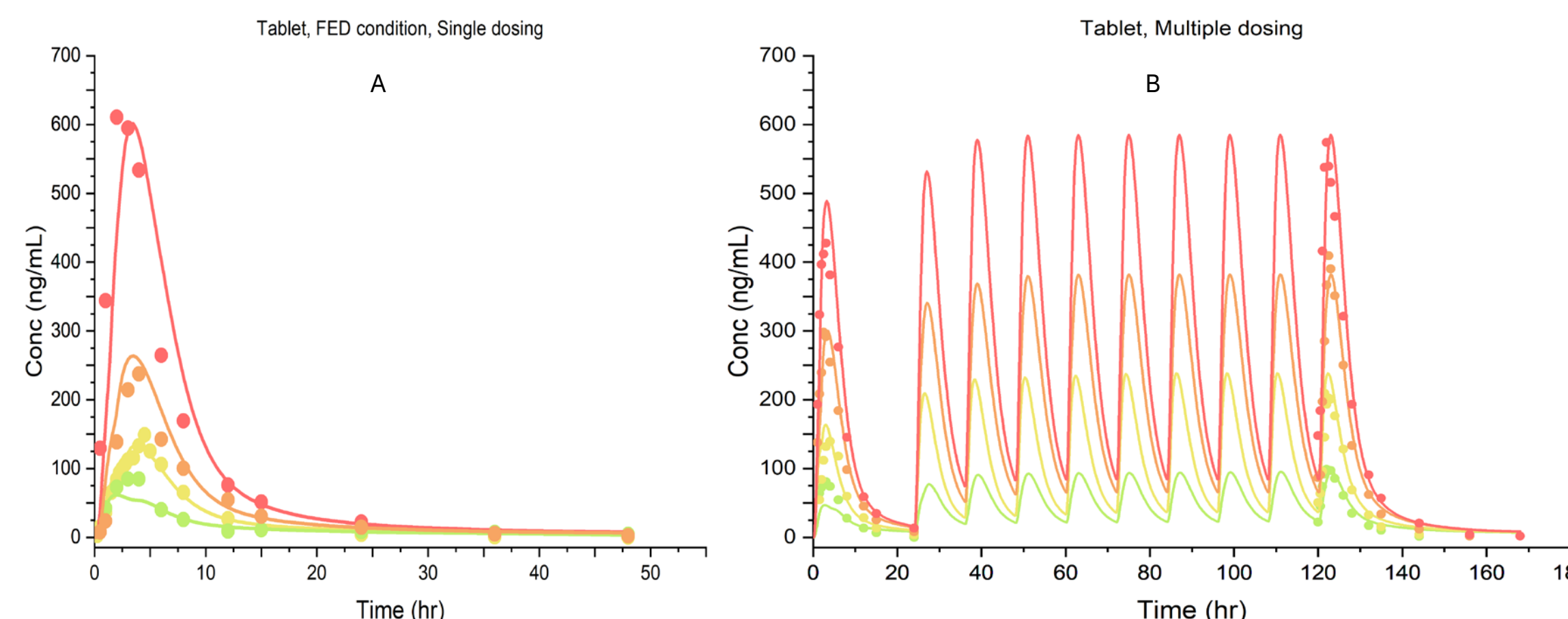
• PBPK modeling and simulation



✓ **Figure 1.** Simulations (lines) and observations (points) of the RIV plasma concentration, urinary and fecal excretion, and metabolism profiles following a single oral administration of 10mg of RIV (solution) to humans in fast condition

Table 1. Key input parameters used for the PBPK model of RIV		
Parameters	Value	Unit
Physicochemical properties		
MW	435.88	g/mol
Lipophilicity (LogP)	1.36	-
Fraction unbound in plasma	5.0	%
Solubility	10	mg/L
ADME parameters		
Absorption		
Specific intestinal permeability	2.65E-7	cm/s
Distribution		
Specific binding with factor Xa (Kd/Koff)	0.005/0.29	(1/s)/nM
Metabolism		
CYP3A4_Km	46.98	μM
CYP3A4_Kcat	2.00	1/min
CYP2J2_Km	19.37	μM
CYP2J2_Kcat	5.11	1/min
CES2_Km	46.98	μM
CES2_Kcat	3.55	1/min
Transport and Excretion		
Renal plasma clearance	0.36	L/h/kg
Dissolution Profile:		
Weibull function (Dissolution time/Shape)		
BAY59-7939 Solution	Dissolved	
BAY59-7939 Tablet	187 min/0.45	
Xarelto IR-Fed State	210 min/1.25	

- Figures 1 and 2** show that the developed PBPK model predict well the clinical data of RIV (plasma concentration profile, urinary and fecal excretion, and metabolism profiles) following a single-/multiple-doses of RIV as in solution/tablet formulations in both fast and fed condition covering a dose range of 5-40mg in humans



✓ **Figure 2.** Simulations (lines) and observations (points) of the RIV plasma concentration following (A) a single-dose and (B) multiple-doses of RIV (tablet) at doses ranged 5-40mg to humans in fed condition

• PopPK modeling and simulation

$$V_{human} = V_{rat} \times \left(\frac{BW_{human}}{BW_{rat}} \right)^{1.00}$$

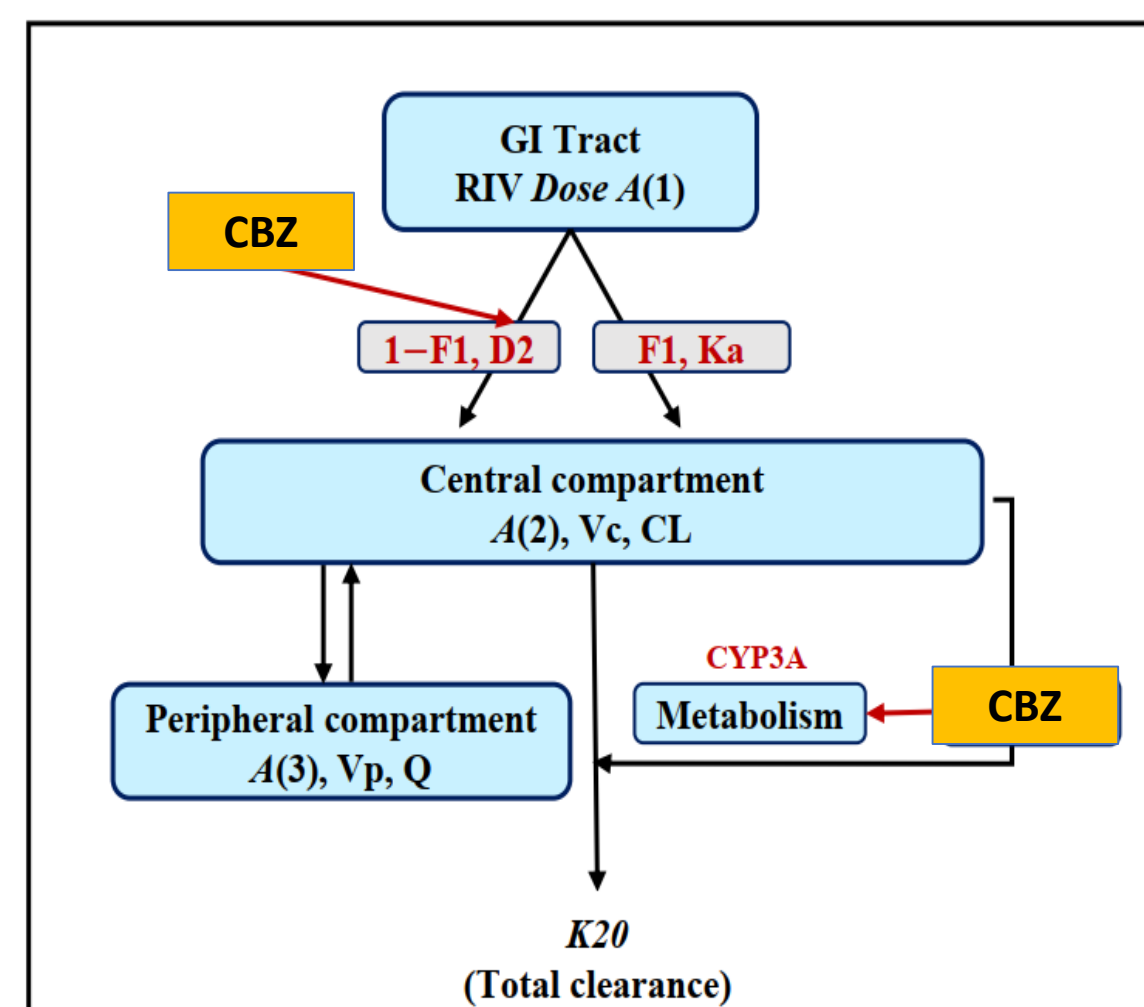
$$CL_{human} = CL_{rat} \times \left(\frac{LBFW_{human}}{LBFW_{rat}} \right)$$

$$CL/F = 0.610 * (1 + FCL_{group})$$
$$D2 = 6.62 * (1 + FD2_{group})$$

- FCL_{group} is 0 and 2.11, and $FD2_{group}$ is 0 and 0.339 for the group of RIV administered without/with CBZ, respectively. Meaning that CL/F and $D2$ of RIV increased by 211% and 33.9% by the CBZ effects, respectively.

- ✓ **Figure 3.** PopPK model for the effect of CBZ on the PKs of RIV and the extrapolation from rats to humans

- D2, duration absorption time (D2) (zero-order absorption)
- Ka, absorption rate constant (first-order absorption)
- CL and Q: apparent systemic clearance and inter-compartment clearance, respectively
- Vc and Vp: central and peripheral volume of distribution



Results

• Prediction of DDI between RIV and CBZ in Humans

- PKs of RIV in humans with/without concomitant administration with CBZ (at their clinical doses, 20mg once daily for RIV and 450mg twice daily for CBZ) were simulated by the developed PBPK and PopPK models

Table 2. Summary of the PK parameters of RIV 20mg once daily in the cases of with/without co-administration with CBZ 450mg twice daily in humans

Parameters of RIV		With CBZ	Without CBZ	Parameter change (With/without CBZ)
PBPK	AUC _{first} (μg/L*h)	1244	1853	0.67
	AUC _{ss} (μg/L*h)	1436	2250	0.64
Modeling and simulation	C _{max-first} (μg/L)	284	384	0.74
	C _{max-ss} (μg/L)	334	460	0.73
PopPK	AUC _{first} (μg/L*h)	616	1292	0.48
	AUC _{ss} (μg/L*h)	775	2157	0.36
Modeling and simulation	C _{max-first} (μg/L)	79	133	0.59
	C _{max-ss} (μg/L)	87	172	0.50

The subscription of “first” and “SS” stand for “the first dose” and “steady-state condition” of RIV, respectively; AUC, area under the concentration-time curve during one dosing interval; C_{max}, maximum concentration

- Table 2** and **Figure 3** show a significant reduction in the exposure of RIV (AUC and C_{max}) after the first dose and at the steady state when RIV was co-administered with CBZ in humans
- AUC and C_{max} of RIV were reduced by approximately (33% and 26%) and (52% and 41%) after the first dose, and (36% and 27%) and (64% and 50%) at the steady state, respectively.

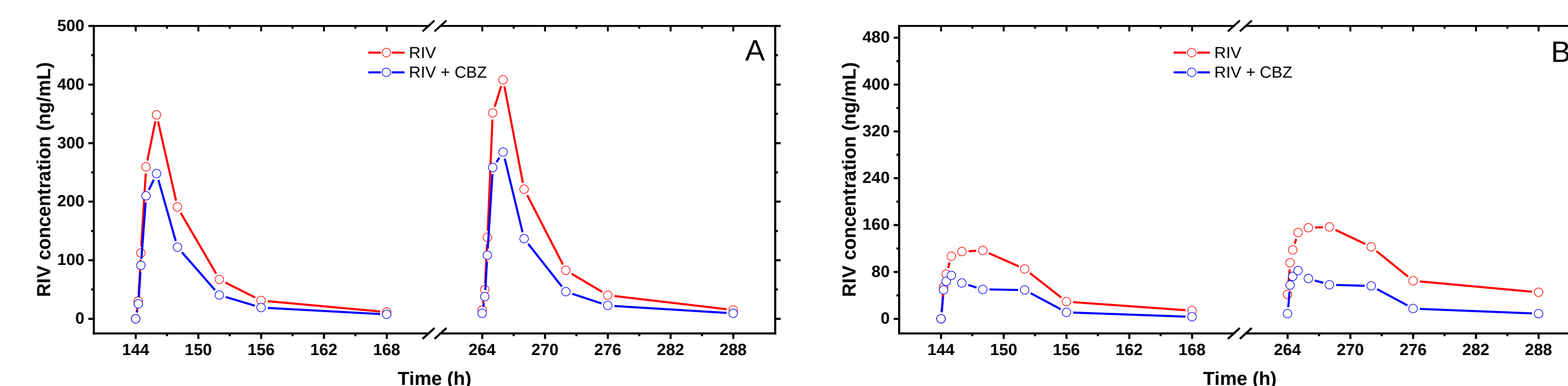


Figure 3. Simulated plasma concentration-time profiles of RIV following oral administration of RIV 20mg once daily with/without co-administration of CBZ at a dose of 450 mg twice a day in humans by (A) PBPK and (B) PopPK modeling and simulation.

Discussions and Conclusions

- The simulation results from both the PBPK and PopPK approaches show that there were significant reductions in the exposures of RIV (10mg, once daily) when the drug was co-administered with CBZ (450mg, twice daily). AUC and C_{max} of RIV were reduced by approximately (33% and 26%) and (52% and 41%) after the first dose, and (36% and 27%) and (64% and 50%) at the steady state, respectively. This reduction was expected to be involved with the CBZ-mediated CYP3A4 induction effect.
- One of the reasons accounting for the difference in the extent of CBZ effect on the PKs of RIV predicted by the PBPK and PopPK models was that the PBPK approach only considered the CYP3A4-mediated effects while the full possible effects of CBZ were considered in the PopPK approach.
- Since RIV and CBZ could be used concomitantly to treat patients with multiple chronic conditions, studies on DDI between these drugs should be conducted in humans to get a full understanding of their safety and effects.

Acknowledgments

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References

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