Physiologically Based Pharmacokinetic (PBPK) Modeling of Rifampicin and Its Application for Drug-Drug Interaction with Midazolam in Adults

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Suvarchala Avvari, Ke Szeto, Viera Lukacova, Michael B. Bolger,

Grace Fraczkiewicz, Revathi Chapa, Tarang Vora

Simulations Plus, Inc., Lancaster, California, USA

PURPOSE

Rifampicin (RIF) is an essential part of tuberculosis therapy and the pharmacokinetics (PK) of RIF has been of interest due to its non-linear and auto-induction behavior. RIF acts as a perpetrator, causing clinically relevant drug-drug interactions (DDIs) via induction and inhibition of multiple metabolic enzymes and transporters.

OBJECTIVE(S)

The purpose was to develop a mechanistic PBPK model for RIF which accounts for all the relevant mechanisms after intravenous (IV) and oral (PO) administration in healthy and tuberculosis (TB) subjects. This model was first validated against single and multiple RIF dosing studies and further validation using sensitive CYP3A4 substrate Midazolam (MDZ) simulating the effect of RIF on MDZ PK.

METHOD(S)

The PBPKPlus™ module in GastroPlus ® v.9.8.2 was used to model the PK of RIF. The Advanced Compartmental Absorption and Transit (ACAT™) model was used to describe the intestinal dissolution, absorption, and metabolism of RIF after PO administration. Human physiologies were generated by the program's internal Population Estimates for Age-Related (PEAR™) physiology™ module. Tissue/plasma partition coefficients (Kps) for all the compounds were calculated using the Lukacova algorithm based on tissue composition along with *in vitro* and *in silico* physiochemical properties. The biopharmaceutical parameters for RIF were obtained from literature or predicted by ADMET Predictor® v10.2. Steady-state volume of distribution (Vdss) was adjusted to match IV noncompartmental Vdss by changing the log P value to 1.5 to calculate the Kp values and then returned to 1.3 for simulations. In addition, the *in vitro* drug permeability from a parallel artificial membrane permeability assay (PAMPA) was converted to human jejunal P_{eff} and then scaled up by 6.2-fold in order to fit the absorption phase [1]. The metabolism of RIF mediated by CYP3A4 was modelled using *in vitro* $K_{m,u}$ and the adjusted V_{max} and the enzyme kinetics were fitted for UGT1A3 [1-2] and the GastroPlus built-in expression levels of both enzymes in gut and liver. To account for the deacetylation of RIF linear systemic clearance of 20 L/h was added to liver. The hepatic uptake of RIF mediated by OATP1B1 was modeled using *in vitro* K_m and V_{max} obtained from literature and a fitted relative activity factor (RAF) of 0.28 [3]. RIF is also a substrate for the hepatic and renal apical efflux transporter MRP2 [4]. The enzyme and transporter K_m and V_{max} values used in the final RIF model are summarized in Table 1. The DDI module in GastroPlus was used to predict the autoinduction and inhibition of RIF and its effect on midazolam PK for varying doses of RIF and MDZ and administration times [13 – 19]. Table 1 presents the *in vitro* and the fitted enzyme and transporter kinetic parameters. Table 2 presents the induction and inhibition parameters of enzymes and transporters for RIF.

RESULT(S)

Table 1: Key Enzyme and Transporter Kinetic parameters for RIF used in GastroPlus® Simulations

Enzyme/Transporter parameter	Value	Reference
CYP 3A4 *in vitro* $K_{m,u}$	16.2 µM (13.3 mg/mL)	[1]
CYP 3A4 V_{max}	0.171 nmol/min/mg Prot.	Fitted
UGT 1A3 $K_{m,u}$	1.62 µM	Fitted
UGT 1A3 V_{max}	0.048 nmol/min/mg Prot.	Fitted
Additional Linear unbound CL_{int} (Liver)	20 L/h	Fitted
OATP1B1 *in vitro* $K_{m,u}$	1.5 ± 0.6 µM	[3]
OATP1B1 *in vitro* V_{max}	9.3 ± 1.3 pmol/min/mg Prot.*	[3]
RAF Factor for OATP1B1	0.28	Fitted
MRP2 *in vitro* $K_{m,u}$	0.87 µM	Assume the MRP2 $K_{m,u}$ is equal to the *in vitro* K_i value
MRP2 V_{max}	13.15 pmol/min/mg MRP2*	Fitted

* Used 0.6 mg protein/million cells to convert transporter Vmax values

Table 2 : Induction and Inhibition parameters of Enzymes and Transporters for Rifampicin

Parameter	Value	Ref
Induction		
***CYP 3A4 *in vitro* $EC_{50,total,Hep}$**	64 nM	[5]
***CYP 3A4 E_{max}**	15	Fitted
***UGT 1A3 *in vitro* $EC_{50,total,Hep}$**	64 nM	[5]
***UGT 1A3 E_{max}**	4.4	[6]
UGT 2B7 *in vitro* $EC_{50,total,Hep}$	64 nM	[5]
UGT 2B7 E_{max}	4.4	[6]
Inhibition		
***CYP 3A4 $K_{i,u}$**	18.5 µM	[7]
***OATP1B1 $K_{i,u}$**	0.62 µM	[8]
***MRP2 $K_{i,u}$**	0.87 µM	[4]
MRP3 $K_{i,total,HLM}$	108 µM	[10]

* Parameters important for the auto-induction and inhibition behavior of Rifampicin

Table 3: Model Development and Validation: Comparison of Simulated and Observed PK Parameters of Rifampicin after (IV) and (PO) Administration in Healthy Subjects and Patients with Tuberculosis.

RIF Dose (mg)	PK Parameter	Obs	Sim	Fold Error	Ref
IV inf 300 mg for 3 hrs	C_{max} (µg/mL)	NA	6.41	NA	[11]
	$AUC_{(0\text{-}inf)}$ (µg.h/mL)	17.6 ± 9.6	37.46	2.12	
IV inf 450 mg for 3 hrs	C_{max} (ug/mL)	NA	9.71	NA	[11]
	$AUC_{(0\text{-}inf)}$ (µg.h/mL)	50.4 ± 21.6	57.55	1.14	
IV inf 600 mg for 3 hrs	C_{max} (ug/mL)	NA	13.1	NA	[11]
	$AUC_{(0\text{-}inf)}$ (µg.h/mL)	64.1 ± 14.2	78.88	1.23	
600 mg, IR tablet	C_{max} (ug/mL)	13.6 ± 3.96	12.15	0.89	[12]
	$AUC_{(0\text{-}inf)}$ (µg.h/mL)	79.8 ± 27.4	75.38	0.94	
IV inf 600mg for 60min Day1	C_{max} (µg/mL)	NA	31.83	NA	[13]*
	$AUC_{(0\text{-}inf)}$ (µg.h/mL)	108.7 ± 31.4	101.8	0.94	
IV inf 600mg for 60min, Day22	C_{max} (µg/mL)	NA	31.8	NA	[13]*
	$AUC_{(0\text{-}inf)}$ (µg.h/mL)	69.9 ± 28.5	65.25	0.93	
600 mg, PO Day 2	C_{max} (µg/mL)	NA	15.74	NA	[13]*
	$AUC_{(0\text{-}inf)}$ (µg.h/mL)	116 ± 29.2	86.71	0.75	
600 mg, PO Day 23	C_{max} (µg/mL)	NA	NA	NA	[13]*
	$AUC_{(0\text{-}inf)}$ (µg.h/mL)	81.3 ± 24.2	50.37	0.62	

*Experimental Data for Subject 4 (Tuberculosis subjects) ; IR – Immediate release

Figure 1 : Goodness of Fit Plot: Comparison of Predicted versus observed DDI plasma Peak concentration ratio (C_{max}) for Midazolam administered alone and with RIF [14 – 19]

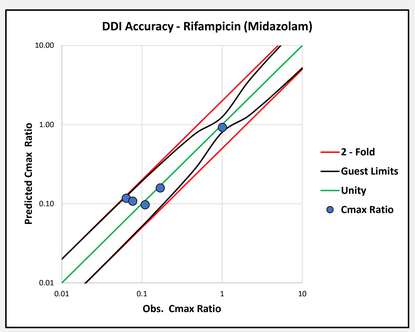
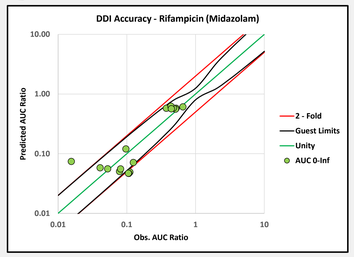


Figure 2 : Goodness of Fit Plot: Comparison of Predicted versus observed DDI AUC_{0_inf} ratio for Midazolam administered alone and with RIF [14 – 19]



Correlation of predicted and observed drug-drug interaction (DDI) ratios for maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) of all the studies. Fig 1 illustrates the DDI Cmax ratios and Fig 2 illustrates the DDI AUC ratios of Rifampicin- Midazolam DDIs. The straight green line marks the line of identity. The red lines indicate 2-fold acceptance limits. The curved black lines show the prediction success limits suggested by Guest et. al (Guest EJ. Et al., DMD. (2011) 39 :170)

Note: Several studies did not report C_{max} values before and after the RIF treatment.

CONCLUSION(S)

This work aimed to develop a RIF PBPK model and demonstrate the use of GastroPlus PBPK approach to predict the potential DDI interactions between RIF and MDZ. The overall results presented in Figures 1 & 2 show that the model accurately predicts the interaction effect of RIF for both IV and PO MDZ dosage forms. In conclusion, the GastroPlus PBPK approach, integrating all relevant physicochemical processes, perpetrator mechanisms, and physiological details is a highly reliable utility to estimate the potential of DDIs.

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