Prediction of Drug-Drug Interactions With a Moderate CYP3A Inducer: Development and Validation of a Physiologically Based Pharmacokinetic Model of Rifabutin

Abstract 1346922

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INTRODUCTION

- Rifabutin, a moderate CYP3A inducer, is a clinically relevant anti-infective agent for patients with B-cell malignancies[1]
- Many anticancer agents are metabolized by CYP3A, and a verified rifabutin physiologically based pharmacokinetic (PBPK) model to predict drug-drug interaction (DDI) would be a useful tool
- We have developed a fully mechanistic PBPK model of rifabutin after oral administration to predict DDI with CYP3A substrate
- The final model was verified against a single dose of 150 mg rifabutin; DDI of rifabutin with fluconazole and midazolam

METHODS

- The full-body mechanistic PBPK model for rifabutin was developed using GastroPlus™ v9.8 (Simulations Plus)
- Physiochemical parameters, absorption, distribution, metabolism, and elimination (ADME) properties of rifabutin, and plasma concentration-time profile for various dose levels of rifabutin were obtained from published literature (**Table 1**)
- Absorption of rifabutin was modeled using the Advanced Compartmental Absorption and Transit (ACAT) model with refinement of precipitation time to describe fraction absorbed and observed plasma concentration profile of single dose of 300 mg rifabutin
- Distribution of rifabutin was assumed to be perfusion limited, and the tissue partition coefficients were calculated with the Lukacova method built-in GastroPlus™
- CYP3A-mediated intestinal and hepatic metabolism of rifabutin was modeled using in vitro maximum velocity (V_{max}) and Michaelis-constant (K_m) values and default CYP3A expression of gut and hepatic tissues (**Table 1**)
  - This in vitro-in vivo extrapolation resulted in an estimated fraction metabolized $(fm)_{CYP3A}$ of 72.1%
- Rifabutin clearance by cholinesterase was added to liver as linear systemic clearance
- Previously reported in vitro CYP3A induction parameters of rifabutin were used to model CYP3A autoinduction and simulate multiple dose plasma profiles of 300 mg rifabutin
- GastroPlus™ models of midazolam and fluconazole were used without modification to verify rifabutin model predicted DDI with fluconazole and midazolam to the observed DDI ratios
- Clinical data used for PBPK model development and verification are summarized in **Table 2**

Table 1. Final Input Parameters for Rifabutin PBPK Model

Parameter (Units)	Value	Reference
MW, (g/mol)	847	2
logD	3.2	2
pKa	1.55 (Base) 8.12 (Base) 6.92 (Acid) 11.04 (Acid) 11.48 (Acid)	ADMET Predictor
Solubility, (mg/ml) (pH)	0.48 (1.2) 3.13 (4.5) 0.054 (6.8)	3
Precipitation time, (s)	15000	Optimized
B/P	0.6	4
f_{up}	0.15	2
P_{eff} (10^{-4} cm/s)	0.275	ADMET Predictor
In vitro parameters		
V_{max} (CYP3A), (p/mol/min/mg protein)	82	5
K_m (CYP3A4), (mmol/L)	8.3	5
Induction parameters[a]		
IND_{max}	8.6	6
$INDC_{50}$, (μM)	0.46	6

B/P, blood to plasma; f_{up}, fraction unbound in plasma; IND_{max}, maximum fold induction; $INDC_{50}$, half maximum-fold induction concentration; logD, logarithm of the distribution coefficient; MW, molecular weight; P_{eff}, effective permeability; pKa, acid-dissociation constant.
[a]Induction parameters are derived from DPX2 cell line.

METHODS (cont.)

Table 2. Clinical study data used in PBPK model development and verification

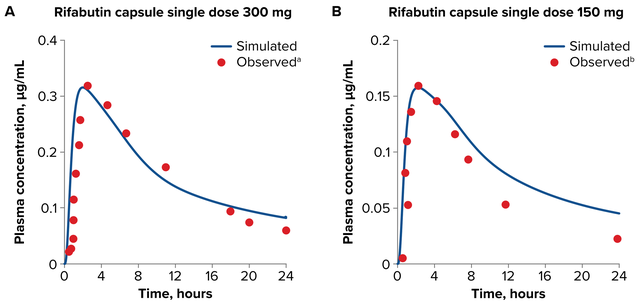
Step	Clinical Scenario	Dose Regimen	Population	Study Description	Reference
Development	300 mg single dose	Single dose 300 mg capsule QD	10 HIV volunteers	Clinical Trial	7
Development	300 mg multiple dose	Multiple dose 300 mg capsule QD 11 days	11 healthy volunteers	DDI between amprenavir and rifabutin	9
Verification	150 mg single dose	Single dose 150 mg capsule QD	12 healthy volunteers	Clinical Trial	8
Verification	DDI	Multiple dose rifabutin 300 mg capsule QD for 10 days in the evening, and 2 mg of midazolam in the morning	20 healthy volunteers	DDI between midazolam and rifabutin	10
Verification	DDI	Multiple dose rifabutin 300 mg capsule QD for 7 days simultaneously with 200 mg of fluconazole	10 HIV volunteers	DDI between fluconazole and rifabutin	11

DDI, drug-drug interaction; HIV, human immuno-deficiency virus; PBPK, physiologically based pharmacokinetic; QD, once daily.

RESULTS

- The base model adequately described plasma concentration of 300 mg single dose (**Figure 1A**) after refinement of precipitation time
- Both predicted and observed (P/O) ratios of maximum plasma concentration (C_{max}) and 0 to 24 hours postdose area under the curve ($AUC_{0\text{-}24}$) for 300 mg single dose and multiple doses were <2 (**Table 3**)
- Rifabutin multiple dose 300 mg simulations were in good accordance with observed data, which confirmed contribution of rifabutin clearance by CYP3A and CYP3A induction by rifabutin (**Figure 2**)
- Verification of rifabutin model was confirmed by good agreement between observed plasma concentration profile and PK parameters for 150 mg single dose with the simulated profile and PK parameters (**Figure 1B** and **Table 3**)

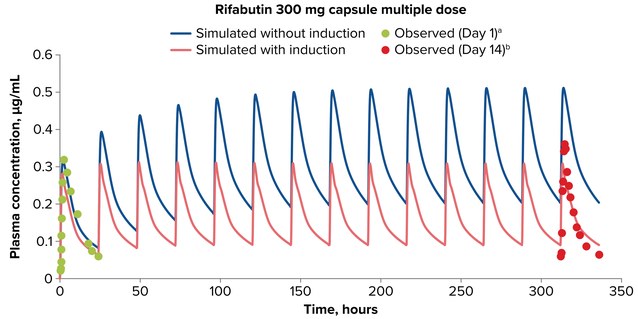
Figure 1. Concentration-Time Profiles of Rifabutin (A) 300 mg and (B) 150 mg



[a]Observed concentration adapted from Gatti et al 1999[7]. [b]Observed concentration adapted from Narang et al 1992[8].

RESULTS (cont.)

Figure 2. Simulated and Observed Plasma Concentration-Time Profiles of Rifabutin



[a]Observed concentration adapted from Gatti et al 1999[7]. [b]Observed concentration adapted from Polk et al 2001[9].

Table 3. Pharmacokinetics of Rifabutin at Different Doses

Dose	PK parameter	Observed	Predicted	P/O ratio
Rifabutin 300 mg single dose	C_{max}, μg/ml	0.34[a]	0.32	0.94
	$AUC_{0\text{-}t}$, μg.h/ml	7.36[a]	6.65	0.90
Rifabutin 300 mg multiple dose	C_{max}, μg/ml	0.38[b]	0.31	0.82
	$AUC_{0\text{-}t}$, μg.h/ml	3.39[b]	3.83	1.13
Rifabutin 150 mg single dose	C_{max}, μg/ml	0.19[c]	0.16	0.84
	$AUC_{0\text{-}t}$, μg.h/ml	2.27[c]	4.04	1.78

$AUC_{0\text{-}t}$, area under the curve from time 0 to the last time point with a measurable concentration.
[a]Observed concentration adapted from Gatti et al 1999[7]. [b]Observed concentration adapted from Jordan et al. 2000[11]. [c]Observed concentration adapted from Narang et al 1992[8].

- DDI of rifabutin with a CYP3A inhibitor, fluconazole, was predicted well for DDI ratios (with and without fluconazole) for C_{max}, and AUC within 2-fold of the observed values (**Table 4**)
- CYP3A induction potential of rifabutin was further verified by excellent agreement between simulated and observed C_{max} and AUC DDI ratios of midazolam administered with rifabutin (**Table 4**)

Table 4. PBPK Model – Predicted Cmax and $AUC_{0\text{-}t}$ DDI Ratios for Rifabutin as a DDI Perpetrator and Victim Compared With Observed Clinical Data

PK parameter	Observed DDI ratio	Predicted DDI ratio	P/O ratio
	Midazolam (with and without perpetrator rifabutin)		
C_{max}	0.46[a]	0.46	1.00
$AUC_{0\text{-}t}$	0.31[a]	0.32	1.03
	Rifabutin (with and without perpetrator fluconazole)		
C_{max}	1.91[b]	1.75	0.91
$AUC_{0\text{-}t}$	1.76[b]	2.07	1.18

[a]Observed data adapted from Lutz et al 2018[10]. [b]Observed data adapted from Jordan et al 2000[11].

CONCLUSIONS

- Base PBPK model for rifabutin was developed using reported in vitro parameters and was refined using published clinical data for 300 mg rifabutin
- PBPK model of rifabutin was verified by comparing observed plasma concentration and simulated profile for 150 mg single dose rifabutin
- Rifabutin CYP3A induction potential was verified by good concordance between simulated and observed DDI ratios of rifabutin as perpetrator with CYP3A-sensitive substrate with midazolam
- The developed and validated PBPK model of rifabutin is appropriate to use as a standard perpetrator to assess the impact of moderate CYP3A4 induction on CYP3A4 metabolized compounds

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DISCLOSURES

MIS: employment with BeiGene
VM, HZ, SS: employment and stock with BeiGene
YCO: leadership and research funding with BeiGene; employment and stock with BeiGene

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