Physiologically Based Pharmacokinetic (PBPK) Modeling of Fexofenadine and Assessment of Transporter DDIs of Fexofenadine with P-gp inducers and inhibitors

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Suvarchala Avvari, Rebecca Graves, Viera Lukacova

Simulations Plus, Inc., Lancaster, California, USA

CONTACT INFORMATION: suvarchala.avvari@simulations-plus.com

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PURPOSE

Fexofenadine (FEX), a H1-receptor antagonist used in the treatment of allergic rhinitis and chronic idiopathic urticaria, undergoes minimal metabolism and transporters play a major role in its absorption and disposition. FEX is frequently used as a probe substrate for P-gp, which plays a significant role in the apical efflux in the intestine, liver and kidneys. FEX is also a substrate for OATP2B1 uptake transporter, which is relatively highly expressed in the apical membrane of enterocytes, and a renal uptake transporter OAT3. The purpose of this project was to develop a PBPK model for FEX which accounts for all the relevant mechanisms impacting FEX pharmacokinetics (PK) after IV and PO administration in healthy Caucasian and Japanese subjects. This model was then validated by predicting the effect of P-gp inducers and inhibitors Rifampicin (RIF), Itraconazole (ITZ), and Verapamil (VPL) on FEX PK.

OBJECTIVE(S)

The objective was to develop a mechanistic PBPK model for FEX which accounts for all the relevant mechanisms after intravenous (IV) and oral (PO) administration in healthy subjects. This model was first validated against single and multiple FEX dosing studies and further validated by predicting DDI with P-gp inducers and inhibitors RIF, ITZ, and VPL.

METHOD(S)

The PBPKPlus™ module in GastroPlus® v.9.8.2 was used to model the PK of FEX. The Advanced Compartmental Absorption and Transit (ACAT™) model was used to describe the intestinal absorption and dissolution of FEX after PO administration. Human physiologies were generated by the program's internal Population Estimates for Age-Related Physiology (PEAR Physiology™) module. The systemic distribution of FEX was described using a whole body PBPK model with a permeability-limited model for kidney and muscle and a perfusion-limited model for the remaining tissues. Tissue/plasma partition coefficients were calculated from tissue composition and compound physiochemical properties using the default methods (Lukacova for perfusion-limited and Poulin and Theil -extracellular for permeability-limited tissues). The permeability-surface area products (PStc) for tissues described by a permeability-limited model were calculated from Specific PStc (Spec.PStc) value (PStc per mL of tissue cell volume) and the individual tissue cell volumes. The Spec.PStc ($6x10^{-4}$ mL/s/mL tissue) was fitted against data from an IV and oral microdose study[1] to correctly capture the tissue distribution. The P-gp efflux was modeled using built-in P-gp expressions in the liver, kidney, and individual intestinal compartments [2,3]. The influx due to OATP2B1 in gut was modeled using the expression levels obtained from literature[4]. The renal uptake due to OAT3 was modeled using built-in expression levels. The experimental *in vitro* K_m values for P-gp, OATP2B1, and OAT3 were taken from the literature[5,6,7]. The Vmax values for P-gp and OATP2B1 were optimized against the C_p-time profiles and the urinary excretion data after FEX 100 µg single dose administered IV and PO[1] and the Vmax value for OAT3 was obtained from literature[7]. To capture reported saturation of P-gp impact on FEX absorption at therapeutic doses [8], the published *in vitro* K_m value for P-gp was reduced by 20% in the final model. To account for the OATP2B1 polymorphic expression in Japanese subjects, an influx V_{max} scale factor of 0.85 was used[9]. The DDI module in GastroPlus was used to predict the effect of RIF, ITZ, and VPL on FEX PK for varying study designs[10-15]. Table 1 summarizes the key physicochemical and biopharmaceutical properties of FEX and Table 2 summarizes the induction and inhibition parameters for perpetrator drugs used in the DDI simulations.

RESULT(S)

Figure 1 presents the Cp-time profiles for a 100ug IV infusion and PO solution dose in healthy Caucasian subjects used for model development. Figure 2 presents the Cmax and AUC predictions for clinical studies used for FEX model development and validation. The model accurately captures FEX PK after single and multiple dose administrations of doses ranging from 0.1 mg to 800 mg, with more than 70% of the predicted Cmax and AUC values within 25% of the observed data and 95% of predictions within 50% of the observed data [1,8, 16-19] . FEX C_p-time profiles before and during co-administration with interacting drugs are also reasonably well predicted over the full range of administered doses and protocols. The predicted Cmax and AUC ratios are mostly within the Guest limits[20] as shown in Figure 3 & 4. It is worthwhile to note the RIF impact, which, depending on the timing of FEX and RIF administration may show a net induction effect (ratio < 1) or net inhibition effect (ratio > 1) and the model accurately captured both these scenarios (orange points in in Figure 3 & 4).

Table 1: Key Physicochemical and Biopharmaceutical Parameters for Fexofenadine Used in GastroPlus Simulations

Parameter	Value
logP	0.5 [21]
Diffusion coefficient	$0.53x10^{-5}$ cm^2/s [a]
pKa	9.462 (base) , 3.931 (acid) [Fitted to pH-solubility profile [22]]
Reference solubility	0.14 mg/mL @ pH = 6.0 [22]
Bile salt solubilization ratio	1802.1 [GastroPlus algorithm]
Geometric mean of B->A & A->B Papp (derived from Caco-2 assay)	9.34×10^{-7} cm/s (Absorption Systems Lighthouse Database)
Human effective permeability (P_{eff})	0.626×10^{-4} cm/s (built-in ABSCa conversion)
Mean precipitation time	20000 sec [Fitted to Cp-time profile]
Blood:plasma concentration ratio (R_{bp})	0.74 [5]
Unbound fraction in plasma (F_{up})	31 % [22] 22% (R-Fexo), 40% (S-Fexo) [14]
Spec PStc	6.0×10^{-4} mL/s/mL tissue [Fitted to Cp-time profile]
Renal Clearance Estimation method	F_{up} * Glomerular Filtration Rate (GFR)
Transporters	
P-gp K_m	25.9 mM [5]
P-gp V_{max} [Fitted]	0.02 mg/s/mg-trans[b] 0.05 mg/s[c]
OATP2B1 K_m	428 mM [6]
OATP2B1 V_{max} [Fitted]	0.06 mg/s[c]
OAT3 K_m	70.2 mM [7]
OAT3 V_{max}	0.012 mg/s/mg-trans[b] [7]

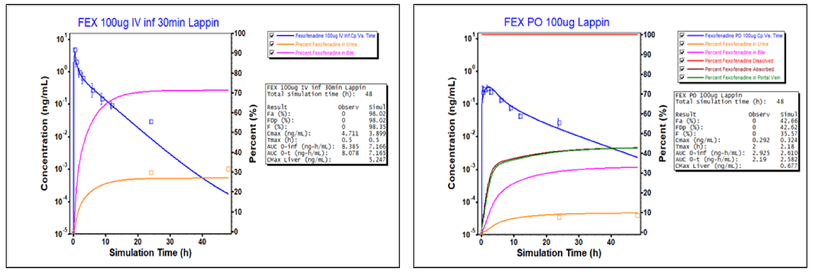
[a] Predicted using ADMET Predictor v10.0
[b] GastroPlus converted V_{max} value in PBPK tissues
[c] GastroPlus converted V_{max} value in Gut

Table 2: RIF, ITZ, and VPL Induction and Inhibition Parameters for Transporters involved in FEX Disposition

Parameter	Value
ITZ	
P-gp IC_{50}, in vitro, u	0.2 µM [23]
OATP2B1, IC_{50}, in vitro, u	3 µM [24]
OAT3 IC_{50}, in vitro, u	30 µM [24]
VPL	
P-gp IC_{50}, in vitro, T	4.5 µM [25]
$F_{u, inc}$	0.515 [25]
RIF	
***CYP3A4**	
EC_{50}, in vitro, u	0.064 µM [26]
E_{max}	15 [Fitted]
K_e, in vitro, u	18.5 µM [27]
***UGT1A3**	
EC_{50}, in vitro, u	0.064 µM [27]
E_{max}	4.4 [Fitted]
***MRP2** K_e, in vitro, u	0.87 µM [28]
***OATP1B1** K_e, in vitro, u	0.07 µM [29]
OATP2B1 IC_{50}, in vitro, u	75 µM [30]
OAT3 IC_{50}, in vitro, u	33 µM [31]
P-gp	
EC_{50}, in vitro, u	0.064 µM [32]
E_{max}	2.2 [33]
K_e, in vitro, u	0.49 µM [32]

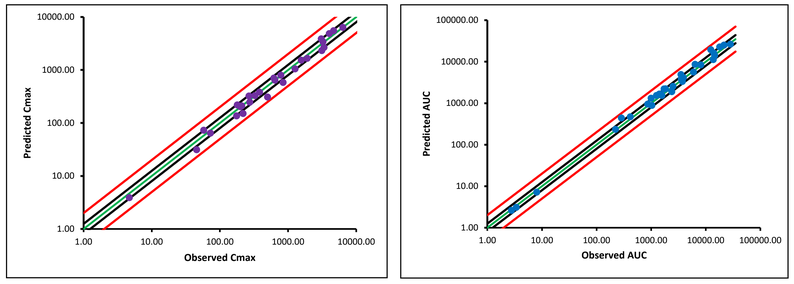
Note : *CYP3A4, UGT1A3, MRP2 and OATP1B1 impact PK of RIF and/or its metabolite and were included in the model to ensure accurate RIF PK prediction

Figure 1 : FEX PBPK Model Development



Cp-time profile for a 100ug IV infusion and PO solution dose of FEX in Healthy Caucasian subjects.
Observed blue squares, simulated blue line of FEX (Lappin et al. 2010). Both plots also displays observed orange squares, and simulated orange line of percent of dose excreted in urine and, simulated percent of dose excreted in bile (pink). The PO plot also displays simulated total amount of dose dissolved (red), absorbed (brown), entered portal vein (green) as a percent of total administered oral dose of FEX.

Figure 2: Predicted versus observed FEX PK parameters (a) C_{max} (b) $AUC_{0\text{-}inf}$ [1, 8, 16-19]



Blue Circles represent $AUC_{0\text{-}inf}$ and Purple Circles represent C_{max}. Red lines (—) represent 2-fold prediction error and Black lines (—) represent 1.25-fold prediction error.

CONCLUSION(S)

The work aimed to develop the FEX PBPK model and validate it as a sensitive substrate model for use in predicting the potential DDI interactions between FEX and P-gp perpetrators. The PBPK approach incorporates all the relevant processes in drug ADME, and all the perpetrator mechanisms. The overall results presented in Figure 3 & 4 show that the model accurately predicts the impact of P-gp perpetrators on FEX PK, and the FEX model can be used to evaluate potential DDI interactions with other P-gp perpetrators.

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Figure 3 : Observed vs Predicted Cmax Ratio for DDI Between FEX and P-gp inducer and inhibitors RIF, ITZ and VPL [14 – 19]

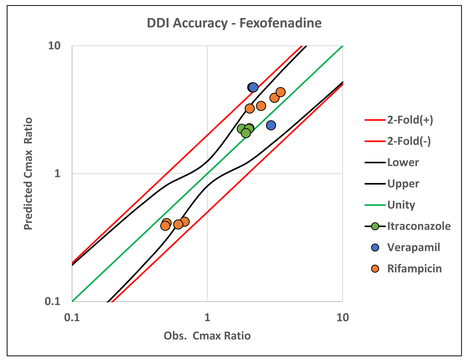

Figure 4 : Observed vs Predicted $AUC_{0\text{-}inf}$ Ratio for DDI Between FEX and P-gp inducer and inhibitors RIF, ITZ and VPL [14 – 19]

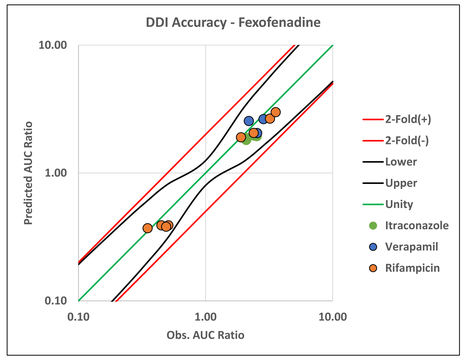

Fig 3 illustrates the DDI Cmax ratios and Fig 4 illustrates the DDI AUC ratios of Fexofenadine- RIF, ITZ, and VPL DDIs. The green, red, and black lines indicate the line of identity, 2-fold acceptance limits, and acceptance limits suggested by Guest et. al (Guest EJ. et al., DMD. (2011) 39 :170)

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