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Efavirenz Physiologically Based Pharmacokinetic Model Development and Validation as a Moderate CYP3A4 Inducer for Drug-Drug Interaction Predictions

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PURPOSE

Efavirenz is an antiretroviral medication used to treat and prevent HIV/AIDS. Efavirenz is eliminated primarily by CYP2B6 and CYP3A4 oxidative metabolism with further glucuronidation to inactive metabolites. Due to substantial induction of both CYP3A4 and CYP2B6 enzyme systems with daily dosing of efavirenz, dose adjustments for many coadministered medications are necessary [1]. Strong, moderate, and weak inducers are drugs that decrease the AUC of sensitive index substrates of a given metabolic pathway by ≥ 80%, ≥ 50% to < 80%, and ≥ 20% to < 50%, respectively [2]. Efavirenz (dosed at 600 mg QD in adults) is a moderate CYP3A4 inducer. As such, a fully validated physiologically based pharmacokinetic (PBPK) model for efavirenz including validated induction potentials could be a useful standard compound for PBPK drug-drug interaction (DDI) simulations. The development of the fully validated PBPK model of efavirenz for use as a moderate CYP3A4 inducer in DDI simulations is presented.

OBJECTIVES

- Develop and validate a PBPK model for efavirenz in humans using PK data obtained from literature.
- Validate the efavirenz PBPK model as a moderate CYP3A4 inducer for DDI predictions using available induction parameters and observed PK data from DDI studies with CYP3A4 substrate(s) reported in literature.

METHODS

GastroPlus® (Version 9.5) [3] was used to develop and validate the PBPK model and run DDI simulations. ADMET Predictor® (Version 8.1) [4] was applied to obtain *in silico* predicted estimates of key physicochemical and biopharmaceutical properties from the chemical structure of efavirenz where experimental values were not found in literature. Plasma concentration versus time (Cp-time) profiles from literature sources were acquired through a process of digitization.

The parameters for the efavirenz PBPK model were derived separately for absorption, distribution, and elimination. The Advanced Compartmental Absorption and Transit (ACAT™) model was used to describe the intestinal dissolution, absorption, and metabolism of efavirenz [5]. The PBPK physiologies, including organ weights, volumes, and blood flows, were generated by the Population Estimates for Age-Related Physiology (PEAR Physiology™) module. Efavirenz tissue distribution was modeled using a perfusion-limited model for all tissues, and tissue/plasma partition coefficients (Kps) were predicted by the default Lukacova method [6].

Mechanistic Assumptions Used for PBPK Model

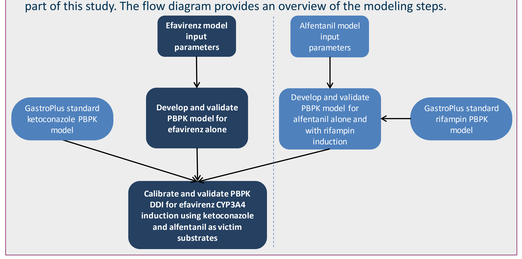
- Efavirenz was absorbed from the gut via a passive diffusion process only.
- Efavirenz is metabolized primarily by CYP2B6 and CYP3A4 isozymes. For modeling purposes, metabolism was described using CYP2B6 and CYP3A4 enzymes only. It was assumed that renal elimination was negligible and was not incorporated in the current model [1].
- The induction of CYP2B6 and CYP3A4 by efavirenz was included in the model to predict steady-state efavirenz PK and for DDI simulations.

Mean particle radius of 5 µm was fitted to match the absorption phase and T_{max} for the evaluated profiles.

Literature values for CYP3A4 and CYP2B6 *in vitro* metabolic K_m and V_{max} in human liver microsomes [7] were used as starting points for efavirenz metabolism. The V_{max} values were subsequently adjusted to match the observed efavirenz Cp-time profiles for both single- and multiple-dose administrations of efavirenz.

The initial values for EC_{50} and E_{max} were obtained from literature [8]. The E_{max} for CYP3A4 was further optimized and validated against data from DDI studies with ketoconazole and alfentanil, respectively. The PBPK model for ketoconazole has been previously developed as a standard CYP3A4 substrate and competitive inhibitor for DDI assessments in GastroPlus.

The PBPK model for alfentanil as a CYP3A4 substrate was also developed and validated as part of this study. The flow diagram provides an overview of the modeling steps.



RESULTS

- Table 1 provides the physicochemical properties that were included in the PBPK model for efavirenz.

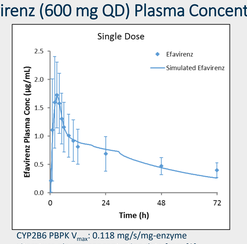
Table 1. Physicochemical and Biopharmaceutical Properties for Efavirenz Model Development

Efavirenz Property	Final Value[a]
logP (at pH = 7.4)	4.6
Aqueous Solubility at pH 6.99	9.0 mg/L
pKa (Acid)	10.2
Permeability: Caco-2 Papp	0.25 cm/s × 10^{5}
Permeability: Human Peff	1.07 cm/s × 10^{4b}
Fraction Unbound in Plasma (Human)	0.22%
Blood/Plasma Concentration Ratio (Human)	0.74
Mean Particle Radius	5 µm
CYP3A4 K_m	3.137 µg/mL
CYP3A4 $V_{max,PBPK}$	0.000562 mg/s/mg-enzyme
CYP3A4 $V_{max,GUT}$	0.2 mg/s
CYP2B6 K_m	3.137 µg/mL
CYP2B6 $V_{max,PBPK}$	0.050 mg/s/mg-enzyme
CYP3A4 E_{max}	9.9
CYP3A4 EC_{50}	1.0 µM
CYP2B6 E_{max}	5.76
CYP2B6 EC_{50}	0.82 µM

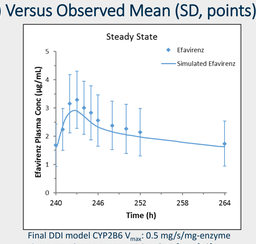
[a] Represents a mix of experimental, predicted, and fitted values.
[b] Caco-2 Papp was converted to human Peff using the built-in ABSCa conversion.

- The developed PBPK model accurately described efavirenz single-dose and steady-state PK after PO administration from a number of published studies. Representative results for a single-dose and a multiple-dose study are presented in **Figure 1**.

Figure 1. Representative Model-Predicted Mean Single-Dose (600 mg) and Steady-State Efavirenz (600 mg QD) Plasma Concentrations (lines) Versus Observed Mean (SD, points)



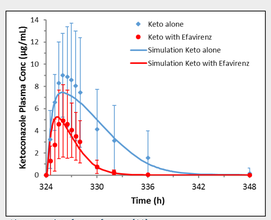
CYP2B6 PBPK V_{max}: 0.118 mg/s/mg-enzyme
Literature plasma concentration data from [9].



Final DDI model CYP2B6 V_{max}: 0.5 mg/s/mg-enzyme
Literature plasma concentration data from [10].

- The utility of the model to predict efavirenz CYP3A4 induction potential was validated by comparing model-predicted exposures for ketoconazole and alfentanil with the clinical data for the following interactions:
  - efavirenz (600 mg QD) and ketoconazole (400 mg single oral dose on Day 12 of efavirenz dosing), **Figure 2**, and
  - efavirenz (600 mg QD) and alfentanil single-dose 43 µg/kg oral or 15 µg/kg intravenous administration on Day 14 of efavirenz dosing, **Figure 3**.

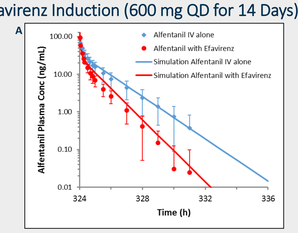
Figure 2. Efavirenz CYP3A4 Induction Calibration: Mean (SD) Observed (points) and Model-Predicted (lines) Ketoconazole Plasma Concentrations Following a Single 400-mg Dose With (red) and Without (blue) Efavirenz Induction (600 mg QD for 14 days)

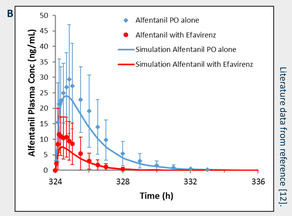


Literature data from reference [11].

RESULTS, CONTINUED

Figure 3. Efavirenz CYP3A4 Induction Validation: Mean (SD) Observed (points) and Model-Predicted (lines) Alfentanil Plasma Concentrations Following Single Doses of Either 15 µg/kg IV Alfentanil (A) or 43 µg/kg PO Alfentanil (B) With (red) and Without (blue) Efavirenz Induction (600 mg QD for 14 Days)





Literature data from reference [12].

- The predicted and observed effects of efavirenz induction on ketoconazole and alfentanil PK parameters are summarized in **Table 2**, indicating good predictions of observed clinical DDI.

Table 2. Efavirenz Induction Model Validation: Summary of Predicted and Observed DDI of Ketoconazole and Alfentanil Single-Dose Administration With and Without Efavirenz Induction (600 mg QD)

		% Reduction With Efavirenz Induction	
Dosage [Reference]	Parameter	Predicted	Observed
Ketoconazole 400 mg PO [11]	C_{max}	29	44
	AUC_{inf}	65	72
Alfentanil 43 µg/kg PO [12]	C_{max}	68	57
	AUC_{inf}	78	78
Alfentanil 15 µg/kg IV [12]	AUC_{inf}	37	46

- A PBPK model for alfentanil was developed for these DDI assessments. The physicochemical and biopharmaceutical properties incorporated into the model are in **Table 3** below.

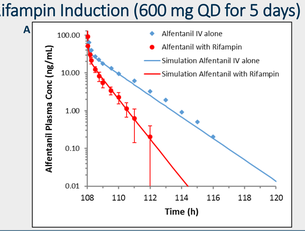
Table 3. Physicochemical and Biopharmaceutical Properties for Alfentanil Model Development

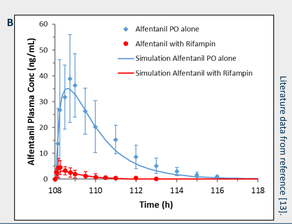
Alfentanil Property	Final Value[a]
logP (at pH = 7.4)	1.5
Aqueous Solubility	0.87 mg/L
pKa (Base)	6.5
Permeability: Caco-2 Papp	1.2 cm/s × 10^{5}
Permeability: Human Peff	2.49 cm/s × 10^{4b}
Fraction Unbound in Plasma (Human)	8.6%
Blood/Plasma Concentration Ratio (Human)	0.66
CYP3A4 K_m	6.419 µg/mL
CYP3A4 $V_{max,PBPK}$	0.00129 mg/s/mg-enzyme
CYP3A4 $V_{max,GUT}$	0.452 mg/s

[a] Represents a mix of experimental, predicted, and fitted values.
[b] Caco-2 Papp was converted to human Peff using the built-in ABSCa conversion.

- The alfentanil PBPK model was validated against clinical study data for single IV and PO alfentanil doses with and without rifampin induction. Representative simulated profiles for 2 such studies are shown in **Figure 4**, demonstrating good fit of the simulated profiles to the observed clinical data.

Figure 4. Alfentanil Model and DDI Validation: Mean (SD) Observed (points) and Model-Predicted (lines) Alfentanil Plasma Concentrations Following Single Doses of Either 15 µg/mL IV Alfentanil (A) or 60 µg/kg PO Alfentanil (B) With (red) and Without (blue) Rifampin Induction (600 mg QD for 5 days)





Literature data from reference [13].

CONCLUSIONS

- **Developed PBPK model for efavirenz accurately reproduces the efavirenz exposures from published single-dose and steady-state studies.**
- **DDI simulations with efavirenz as the perpetrator with either ketoconazole or alfentanil as the victim accurately predict the observed exposures due to the induction of CYP3A4 by efavirenz.**
- **Developed and validated PBPK model for efavirenz is suitable to be used as a standard perpetrator to evaluate the impact of moderate CYP3A4 induction on CYP3A4-metabolized compounds.**
- **Developed and validated PBPK model for alfentanil is suitable to be used as a standard victim for DDI interaction predictions with CYP3A4 inducers.**

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