The Effect of CYP2B6 Phenotype on the Clearance and Autoinduction of Efavirenz in Healthy Subjects and the Subsequent Impact on Exposure

Michael A Heathman[1,2], Ingrid F Metzger[3], Jessica Lu[1], Brandon T. Gufford[1], Zeruesenay Desta[1], Blessed Winston Aruldhas[4]

1. *Division of Clinical Pharmacology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN*
2. *Metrum Research Group, Boston, MA, USA*
3. *Universidade de Brasília, Brazil*
4. *Department of Pharmacology and Clinical Pharmacology, Christian Medical College, Vellore, India*

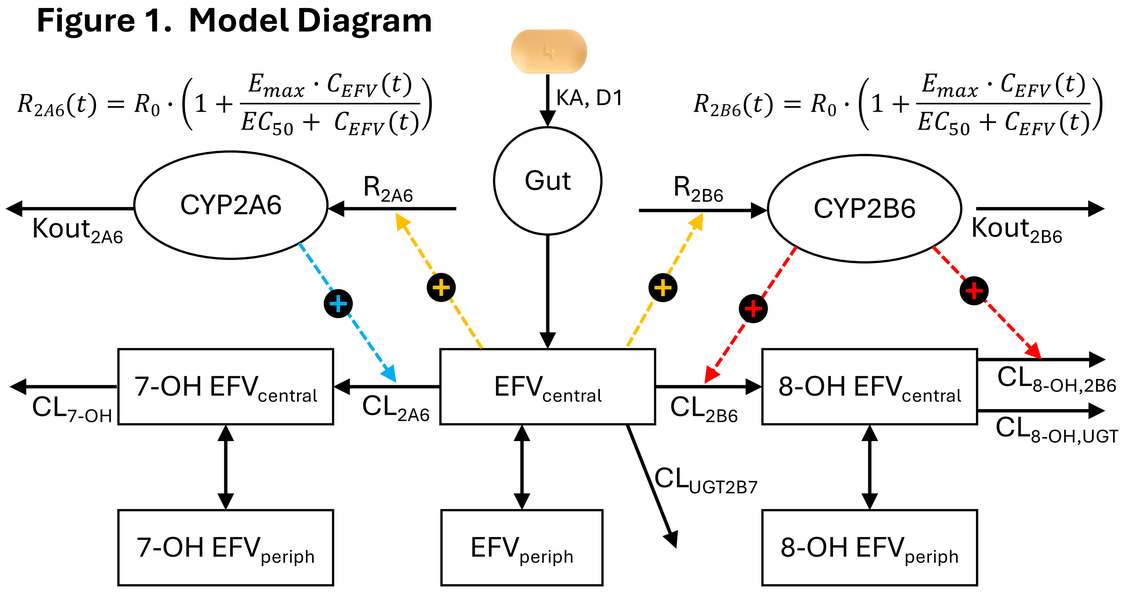
Objectives

The antiretroviral drug efavirenz (EFV) is metabolized primarily by CYP2B6, to form 8-OH EFV, and also by CYP2A6, to form 7-OH EFV. Upon chronic administration, EFV induces both CYP2B6 and CYP2A6, leading to autoinduction of its metabolism. Variability in the extent of autoinduction contributes to the variability of EFV pharmacokinetics (PK), which in turn determines clinical response, adverse events, and drug interactions. The objective of this analysis was to quantify the impact of CYP2B6 phenotype on EFV autoinduction and subsequent exposure, using population PK modeling.

Methods

Samples (n=4594) from 135 healthy volunteers were collected up to 144 hours post-dose following a single 600 mg dose of EFV and after once daily treatment with 600 mg/day for 17 days. EFV and its 8-OH and 7-OH metabolites were quantified using LC/MS/MS. CYP2B6 genotype was obtained and phenotype classified as normal (NM), intermediate (IM), or poor metabolizer (PM). A population PK model was developed for EFV and its metabolites using NONMEM and the SAEM estimation method.

Figure 1. Model Diagram



Results

Two-compartment models were used to describe the PK of EFV and its metabolites (Figure 1). EFV absorption was described using a sequential zero- and first-order process. The central volume of both metabolites were set equal to that of EFV, due to lack of identifiability. Exponential inter-individual variability was incorporated on all PK parameters. Residual variability was described using a proportional model for all three analytes.

Independent enzyme turnover models were used to characterize the autoinduction of CYP2B6 and CYP2A6. The enzyme models were parameterized in terms of maximum induction, concentration of half-maximal induction, and enzyme turnover rate. The effect of CYP2B6 phenotype was evaluated on formation rate of 8-OH EFV and maximum induction of CYP2B6. IM and PM were both found to decrease the formation rate of 8-OH EFV by 9 to 10%. IM and PM were found to decrease the maximum induction of CYP2B6 by 54% and 93%, respectively (Table 1).

Table 1. Final Model Parameters

Parameter	Estimate	95% CI
Structural Parameters		
KA (1/h)	0.165	(0.144, 0.190)
D1 (h)	1.74	(1.59, 1.91)
CL-EFV,2B6 (L/h)	3.64	(3.33, 3.98)
CL-EFV,2A6 (L/h)	0.0947	(0.0788, 0.114)
CL-EFV,UGT (L/h)	0.0504	(0.0453, 0.0560)
VC-EFV (L)	3.99	(3.44, 4.63)
VP-EFV (L)	520	(476, 567)
Q-EFV (L/h)	28.3	(24.7, 32.4)
CL-8OH,2B6 (L/h)	0.758	(0.700, 0.819)
CL-8OH,UGT (L/h)	5.44	(4.97, 5.94)
VP-8OH (L)	133	(120, 147)
Q-8OH (L/h)	5.62	(5.29, 5.97)
CL-7OH (L/h)	3.39	(2.96, 3.87)
VP-7OH (L)	29.4	(22.6, 38.2)
Q-7OH (L/h)	2.25	(2.08, 2.43)
Auto Induction		
EMAX-2B6	15.5	(12.7, 19.0)
KOUT-2B6 (1/h)	0.00684	(0.00630, 0.00744)
EC50-2B6 (nM)	32000	(29100, 35100)
EMAX-2A6	4.22	(3.33, 5.33)
KOUT-2A6 (1/h)	0.00982	(0.00895, 0.0108)
EC50-2A6 (nM)	12500	(11400, 13600)
Effect of Phenotype		
CL-EFV,2B6 ~ IM (% reduction)	9.72	(20.8, -2.85)
CL-EFV,2B6 ~ PM (% reduction)	9.06	(26.6, -12.7)
EMAX-2B6 ~ IM (% reduction)	53.5	(65.6, 37.1)
EMAX-2B6 ~ PM (% reduction)	93.2	(96.3, 87.6)

Parameter	Estimate	95% CI	Shrinkage (%)
Inter-Individual Variability			
IIV ~ KA (%CV)	89.3	(71.2, 107)	6.38922
IIV ~ D1 (%CV)	54.1	(44.3, 63.0)	7.5678
IIV ~ CL-EFV,2B6 (%CV)	35.6	(27.1, 42.7)	7.62049
IIV ~ CL-EFV,2A6 (%CV)	137	(109, 168)	3.60834
IIV ~ CL-EFV,UGT (%CV)	15.1	FIXED	
IIV ~ VC-EFV (%CV)	88.6	(66.3, 110)	7.01611
IIV ~ VP-EFV (%CV)	53.7	(47.6, 59.5)	1.34296
IIV ~ Q-EFV (%CV)	86.5	(59.7, 112)	6.35407
IIV ~ CL-8OH,2B6 (%CV)	15.1	FIXED	
IIV ~ CL-8OH,UGT (%CV)	49.4	(41.8, 56.3)	3.92538
IIV ~ VP-8OH (%CV)	36.9	(20.3, 48.9)	30.3855
IIV ~ Q-8OH (%CV)	15.1	FIXED	
IIV ~ CL-7OH (%CV)	74.0	(59.8, 87.3)	13.358
IIV ~ VP-7OH (%CV)	93.7	(48.1, 137)	25.4937
IIV ~ Q-7OH (%CV)	15.1	FIXED	
IIV ~ EMAX-2B6 (%CV)	83.9	(53.3, 112)	9.45162
IIV ~ KOUT-2B6 (%CV)	15.1	FIXED	
IIV ~ EC50-2B6 (%CV)	15.1	FIXED	
IIV ~ EMAX-2A6 (%CV)	171	(137, 209)	9.94856
IIV ~ KOUT-2A6 (%CV)	15.1	FIXED	
IIV ~ EC50-2A6 (%CV)	15.1	FIXED	
Residual Unexplained Variability			
RUV ~ EFV (%CV)	25.8	(25.2, 26.4)	
RUV ~ 8-OH EFV (%CV)	28.0	(27.3, 28.6)	
RUV ~ 7-OH EFV (%CV)	29.9	(29.2, 30.5)	

Results (continued)

Simulations were conducted to explore the effect of CYP2B6 phenotype on EFV exposure (Figures 2 and 3). The simulations showed that concentrations in NM and IM subjects peak after 5 to 10 days and then decline, while concentrations in PM subjects continue to accumulate for 2 to 3 weeks. The commonly accepted minimum effective concentration of EFV in adults is 1 µg/mL at 12 hours post-dose, while concentrations over 4 µg/mL are associated with CNS side effects.[1] The model predicted that steady-state concentrations 12 hours post-dose exceed 4 µg/mL in 58% of PM subjects.

Figure 2. Predicted Effects of Autoinduction

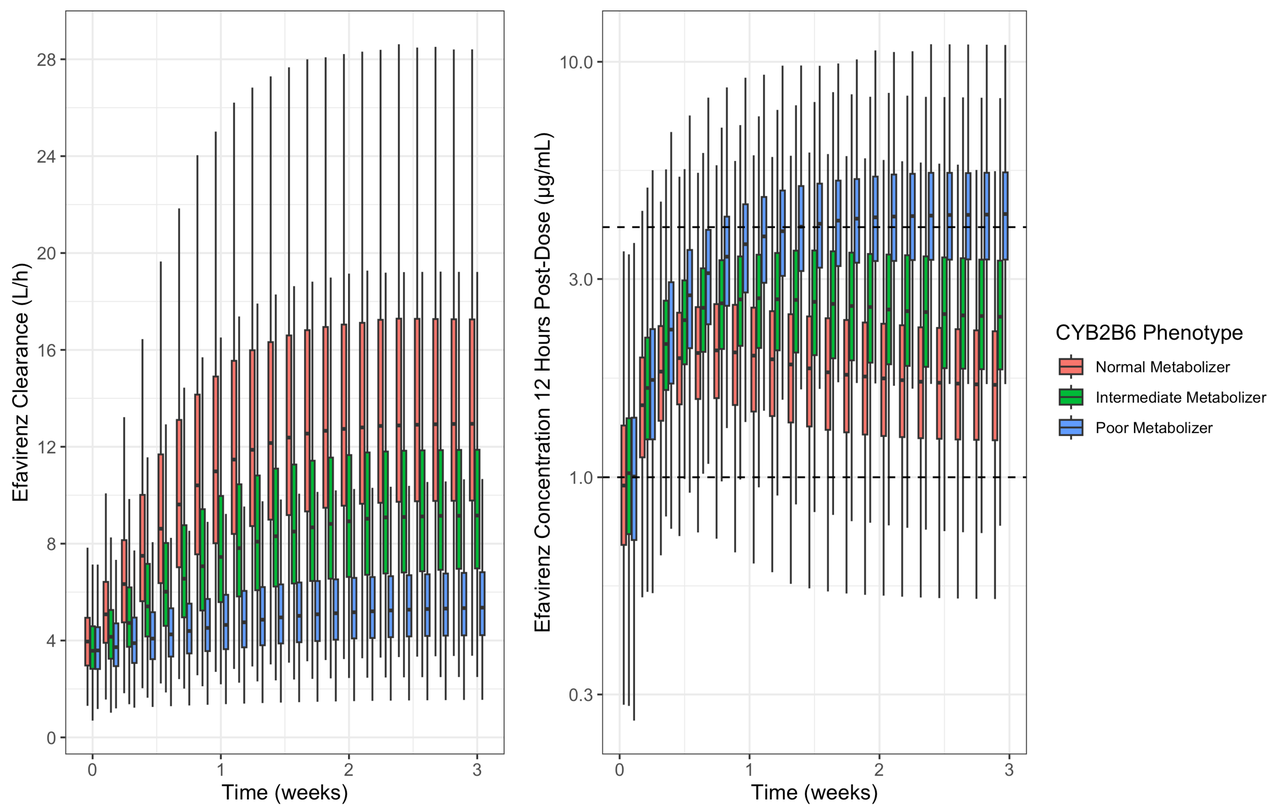
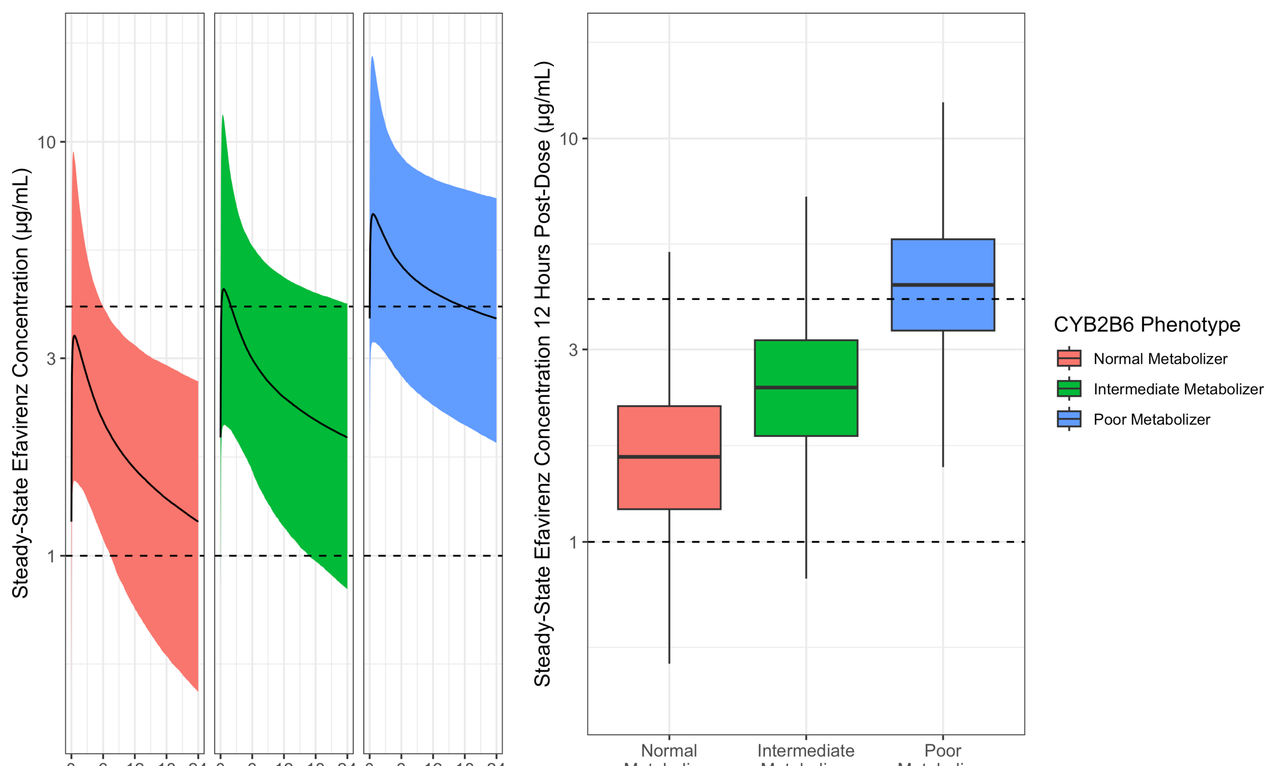


Figure 3. Predicted Steady-State EFV Concentrations



Conclusions

CYP2B6 polymorphisms significantly attenuate the autoinduction of EFV clearance, while also impacting clearance itself. Accounting for these differences in autoinduction between CYP2B6 polymorphisms may allow better understanding of optimal treatment regimens in patients with IM or PM status.

References

[1] Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. AIDS. 2001;15(1):71-75.

INDIANA UNIVERSITY SCHOOL OF MEDICINE

METRUM RESEARCH GROUP