American Society for Clinical Pharmacology and Therapeutics 2012 Annual Meeting

Pharmacokinetic and Pharmacodynamic Analysis of Efavirenz Dose Reduction Using a Physiologically-Based Dynamic Model

Marco Siccardi
siccardi@liverpool.ac.uk
T +44 151 794 5553
F +44 151 794 5656

Marco Siccardi[1], Lisa Almond[2], Alessandro Schipani[1], Chantal Csajka[3], Catia Marzolini[4], Duncan Edwards[2], Saye Khoo[1], Andrew Owen[1], David Back[1].

1 - Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK. 2- Simcyp Limited, Sheffield, UK

3 - Division of Clinical Pharmacology and Toxicology, Département de Médecine, Hôpital de Beaumont, Lausanne, Switzerland. 4 - Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland

Abstract

Background: Efavirenz (EFV) pharmacokinetics (PK) is characterized by large inter-patient variability and a correlation between plasma exposure and efficacy has been described. The aim of this study was to develop a physiologically-based model to simulate EFV PK and PD in virtual human subjects.

Materials and Methods: *In vitro* data describing the chemical properties, ADME of EFV and the effect of CYP2B6 516 genotype on CYP2B6 protein expression in liver tissue were obtained from published literature. These data were used to simulate EFV (600mg once daily) PK using Simcyp Simulator. Simulated PK parameters, such as Ctrough, Cmax, AUC, and the impact of 516G>T genotype were compared with clinical observations. PK/PD was characterised using data from Csajka et al. and Marzolini et al. and a significant correlation between C8-16hr and viral suppression was identified. This was incorporated into the IVIVE and the effect of dose reduction to 400mg once daily on PK and viral load simulated.

Results: In a virtual Caucasian cohort of 500 patients the simulated Ctrough was equal to 2275 ± 2045 ng/ml and Cmax 3438 ± 2246 ng/ml. Clearance (CL/F) was 15.6 l/hr for 516 GG, 11.4 l/hr for 516GT and 6.4 l/hr for 516 TT. Overall, the mean (95% CI) probability of achieving viral suppression was 80% (44-99) and 75.5% (33-99), 81.6% (41-99), 88.8% (61-99) in patients with 516 GG, 516 GT, 516 TT genotypes, respectively. Following dose reduction to 400 mg, overall mean probability of viral suppression was decreased to 73.4% (34-99), and to 69.2% (26-97), 76.7% (34-99), 84.9% (53-99) for 516 GG, 516 GT, 516 TT genotypes, respectively.

Conclusions: The model developed predicted the PK and PD of EFV in individuals with different CYP2B6 genotypes. These simulations indicate that genotype-guided dose reduction could be used in patients without compromising viral suppression.

Introduction

The pharmacokinetics (PK) of efavirenz (EFV) is characterized by large inter-patient variability [1]. CYP2B6 is the main enzyme responsible for EFV metabolism and CYP2B6 polymorphisms can markedly affect EFV exposure, with 516G>T (rs3745274) considered to be the main genetic variant [2]. The relationship between EFV PK and pharmacodynamics has been investigated in several studies, a putative MEC of 1 mg/L and upper concentration for toxicity of 4 mg/L have been suggested [3].

The *in vitro in vivo* extrapolation (IVIVE) is a “Bottom-Up” approach to model pharmacokinetics of drugs using *in vitro* data such as physiochemical characteristic of the drugs, intrinsic clearance in human liver hepatocytes and transporter affinity. The Simcyp Simulator is a platform for IVIVE and can simulate oral absorption, tissue distribution, metabolism and excretion of drugs in virtual populations (Figure 1).

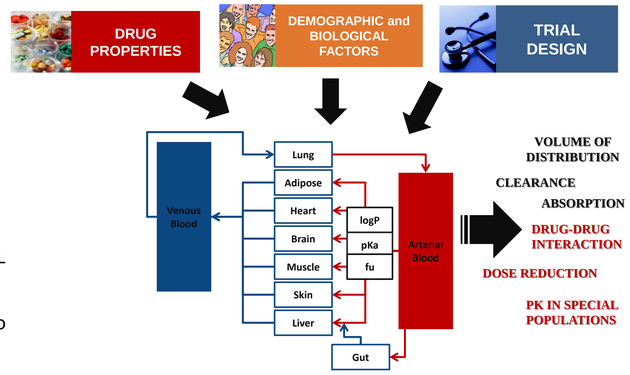

Figure 1. Known variability in demographic and biological (genetic and environmental) factors is incorporated in PBPK models with drug-specific physicochemical properties. Several dosing strategies can be included in the simulation and different cohorts can be selected.

Methods

In vitro data describing the physiochemical properties, absorption and metabolism of EFV and the effect of CYP2B6 516 genotype on CYP2B6 protein expression in liver tissue were obtained from published literature or quantified with standard methods (Table 1-2) [4-9]. The volume of distribution and penetration into tissues was predicted with the full PBPK using the Poulin and Theil method [10]. To investigate the effect of EFV PK on viral suppression data from Csajka et al and Marzolini et al was used [1, 3]. Patients with a viral load determination within 3 months of commencing therapy were included in the analysis. Therapeutic failure was classified as two consecutive viral load determinations above 50 copies/ml. Demographic characteristics and mean EFV concentrations between 8 and 16 hours ($_{C8\text{-}16hr}$) after dose, which is the most common timing for sampling in the clinical setting, were included in a logistic regression analysis to identify predictors of viral suppression.

Table 1. Drug properties

Molecular weight	315.7
logP	4.6
Protein binding	98%
Caco-2 Papp	2.5 (10^{-6} cm/s)
EFV metabolism to 8-OH	
rCYP2B6 Cl_{int}	0.55 µL/min/pmol [4]
rCYP1A2 Cl_{int}	0.07 µL/min/pmol [4]
rCYP2A6 Cl_{int}	0.08 µL/min/pmol [4]
rCYP3A4 Cl_{int}	0.007 µL/min/pmol [4]
rCYP3A5 Cl_{int}	0.03 µL/min/pmol [4]
EFV metabolism to 7-OH	
rCYP2A6	0.05 µL/min/pmol [5]
EFV metabolism to glucuronide	
rUGT2B7	0.05 µL/min/pmol [6]
CYPs induction	
CYP2B6 Ind_{max}	6 [7]
CYP3A4 Ind_{max}	1.5 [8]

Table 2. Effect of *CYP2B6* 516G>T on hepatic CYP2B6 expression

516 GG (55%)	
CYP2B6 expression	24 pmol/mg-prot [9]
516 GT (38%)	
CYP2B6 expression	17 pmol/mg-prot [9]
516 TT (7%)	
CYP2B6 expression	8 pmol/mg-prot [9]

Aim

To develop and assess an IVIVE model for EFV PK and PD. The effect of dose reduction (from 600 to 400mg) on PK and PD investigated in virtual subjects with different CYP2B6 genotypes.

Results

In a virtual cohort of 500 individuals the simulated PK parameters were in good agreement with published data as shown in Table 3.

Table 3. Main simulated PK parameters and comparison with reference values

	Simulated	Reference [11]
C_{max} (mg/L)	3457 ± 1964	4063 ± 1165
C_{trough} (ng/mL)	2219 ± 1784	1764 ± 1008
AUC (ng/mL·hr)	67010 ± 47204	57960 ± 22995

The 516 GT and 516 TT genotypes were correlated with a CL/F decrement of 26% and 54%, respectively. In a recent population pharmacokinetic study, the effect of 516 GT was to decrease EFV clearance by 22% and 57% for 516 TT [12]. 93 patients could be included in the analysis with 14 virologic failures. 65 patients (68%) were male, the median age was 38 years (IQR, 33-44), the median body weight was 66 kg (IQR, 60-75 kg), and. EFV plasma exposure was identified as the only independent predictor of viral suppression via logistic regression analysis, for log10 $C_{8\text{-}16hr}$ the odds ratio (OR) = 22.6 (95% CI, 1.37-372), p =0.029.

Simulated PK variables for a dosing of 400 mg at steady state for a cohort of 500 virtual patients were: C_{trough} was equal to 1480 ± 1190 ng/ml, C_{max} 2305 ± 1309 ng/ml, AUC 44673 ± 31470 ng/mL.h.

Table 4. Simulated pharmacokinetic variables and probability of viral suppression at steady state, at a dose of 600 mg and 400mg for a cohort of 500 virtual patients

	dose	C_{max} (ng/ml)	C_{trough} (ng/ml)	AUC (ng.h/ml)	Probability of achieving viral suppression (95%CI)
516 GG	600 mg	3022 ± 1692	1873 ± 1487	59797 ± 41164	0.755 (0.43-0.98)
	400 mg	2014 ± 1128	1100 ± 1040	39864 ± 27442	0.734 (0.30 – 0.96)
516 GT	600 mg	3919 ± 2322	2752 ± 2131	82539 ± 57760	0.816 (0.47-0.99)
	400 mg	2613 ± 1548	1817 ± 1420	55027 ± 38507	0.767 (0.37-0.98)
516 TT	600 mg	5160 ± 2731	3917 ± 2555	114151 ± 68590	0.888 (0.61-0.99)
	400 mg	3440 ± 1821	2612 ± 1703	76100 ± 45726	0.849 (0.51-0.99)

Discussion

The IVIVE model predicted the PK and PD of EFV in individuals with different CYP2B6 genotypes. The PK of EFV was correctly predicted based only on *in-vitro* data and this model is a paradigm example of the IVIVE potential.

Our study has some limitations, since EFV is metabolised by several CYPs, the inclusion of all genetic variants and a more detailed description of metabolism and induction of enzyme expression could improve the accuracy of clearance simulation. In addition the role of transporters in the regulation of EFV disposition has not been fully investigated and clarification of the role of transporters in the disposition of EFV might help to explain part of the variability observed in EFV PK. This simulation approach can be used to investigate clinically relevant ‘what-if’ questions, such as the whether genotype-based dose reduction strategies are feasible to manage inter individual differences in exposure. The current model has been developed using a PK/PD equation derived for patients treated with NRTIs such AZT, d4T and ddI (1). Currently TDF and FTC are commonly prescribed with EFV and consequently the effect of these NRTIs may be underestimated in the current model.

Conclusion

These simulations indicate that genotype-guided dose reduction could be used in patients without compromising viral suppression and our model could form the basis of dose selection in prospective clinical trials.

References

1 - Csajka, C. et al. Clin Pharmacol Ther. 2003; 73, 20-30.
2 - Arab-Alameddine, M. et al. Clin Pharmacol Ther. 2009; 85, 485-94.
3 - Marzolini, C. et al. AIDS. 2001; 15, 71-5.
4 - Ward, BA. et al. Pharmacol Exp Ther. 2003; 306: 287-300
5 - Ogburn, ET. et al. Drug Metab Dispos. 2010; Jul;38(7):1218-29
6 - Bélanger , AS. et al. Drug Metab Dispos. 2009; Sep;37(9):1793-6.
7 - Faucette et al. J Pharmacol Exp Ther. 2007; 320: 72-80.
8- Mouly, S. et al. Clin Pharmacol Ther. 2002; 72(1):1-9.
9- Lang ,T. et al. Pharmacogenetics. 2001;11(5):399-415.
10- Poulin, P. et al. J Pharm Sci. 2002; 91, 129-56.
11 - Nyakutira, C. et al. Eur J Clin Pharmacol. 2008; 64, 357-65.
12 - Vrouenraets SM et al. Expert Opin Pharmacother. 2007 Apr;8(6):851-71.