Population Pharmacokinetics of Efavirenz and Impact of MDR-1, CYP2B6 and CYP3A5 Polymorphisms

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BACKGROUND

Efavirenz, an antiretroviral drug metabolized by polymorphic enzymes, exhibits between-subject variability causing varied clinical response. Lower and higher plasma concentrations among HIV patients result into virologic failure and central nervous system related toxicity, respectively. Factors for efavirenz pharmacokinetic variability, which include sex and ethnicity, are poorly understood.

OBJECTIVES

In this study we aimed to study the effects of pharmacogenetic polymorphism in CYP2B6, CYP3A5 and MDR-1 on the efavirenz population pharmacokinetics among Ugandans.

METHODS

A total of 121 healthy subjects were included in the study. Blood samples were collected from 32 of the subjects at 0, 1, 2, 4, 8, 24, 48 and 72 hours after a single oral dose of 600 mg efavirenz. For the 89 additional subjects, samples were collected at 4 and 24 hours after dose. Efavirenz concentrations in plasma were determined by reverse phase HPLC with UV-detection. Study participants were genotyped for 26 single nucleotide polymorphisms in CYP2B6 (n=7), CYP3A5 (n=5), and MDR-1 (n=14) genes by mini-sequencing and PCR-RFLP. To explore the influence of covariates on the efavirenz population pharmacokinetics, the data was analyzed using a non-linear mixed effects modelling approach in NONMEM. First, the pharmacokinetic covariate model was developed with all demographic (sex, age and body weight) and biochemical (albumin, ALT, urea and serum creatinine) variables. Eventually, covariates expressing pharmacogenetic polymorphism were added to the pharmacokinetic/pharmacogenetic model one by one through stepwise forward inclusion followed by backward elimination. Pharmacogenetic covariates were assumed to affect either CL/F or the relative bioavailability (F_{rel}).

RESULTS

The final dataset comprised a total of 402 efavirenz concentration-time observations. The pharmacokinetics of efavirenz were described by a two-compartment model with zero- followed by first-order absorption (Figure 1). Basic goodness of fit plots are visualized in Figure 2. The estimate (95% CI) of efavirenz apparent clearance was found to be 4 (3.5, 4.5) L/h for wild-type genotypes. In the whole population, the unexplained between-subject variability (CV%) in apparent clearance was estimated to 28%.

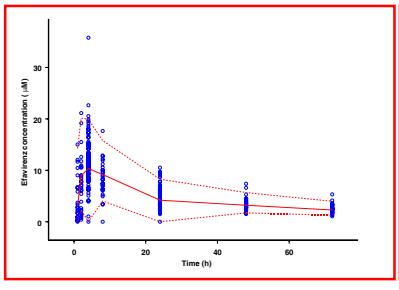

Figure 1. Predictive check of the final efavirenz pharmacokinetic/pharmacogenetic model.

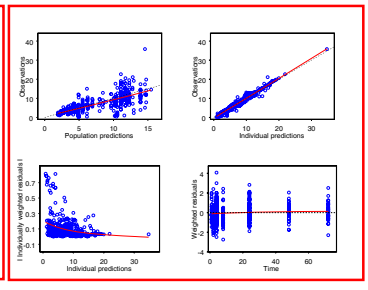

Figure 2. Basic goodness of fit.

The inclusion of CYP2B6 (516G>T (*6) and *11) polymorphisms in the model explained 11% and 3% of the between-subject variability and 'poor metabolisers' were observed to have 22 and 19% lower clearance than 'extensive metabolisers', respectively. Sex as a covariate reduced unexplained between-subject variability in the peripheral volume of distribution from 41 to 24%, while MDR-1 (rs exon 29) reduced the between-subject variability from 29 to 19% in efavirenz relative bioavailability, which was 26% higher in mutant subjects. The peripheral volume of distribution was two-fold higher in females compared to males. Pharmacokinetic parameter estimates are presented in Table 1. Simulated concentration-time courses after a single dose of efavirenz administrated to typical male and female homozygous mutant CYP2B6*6, *11 and MDR-1 subjects and to typical subjects with wild-type genotypes are depicted in Figure 3. The relationship between selected covariates and the individually predicted parameter estimates are displayed in Figure 4.

Pharmacokinetic/pharmacogenetic model		
Parameter	Mean (95% CI)	CV% (95% CI)
CL/F (L/h)	4.00 (3.47, 4.53)	14.0 (2.8, 25.2)
Effect of CYP2B6*6 (T/T)	-0.209 (-0.386, -0.032)	
Effect of CYP2B6*11 (G/G)	-0.199 (-0.329, -0.0691)	
Vc/F (L)	19.1 (7.46, 30.7)	99.5 (49.4, 132)
Vp/F (L)	155 (131, 179)	27.9 (14.8, 36.7)
Effect of sex	2.08 (1.64, 2.52)	
Q/F (L/h)	13.7 (6.1, 21.3)	32.1 (20.5, 40.5)
k_a (h^{-1})	0.146 (0.0558, 0.236)	19.7 (8.6, 30.8)
D (h)	1.07 (0.758, 1.38)	69.7 (15.3, 97.4)
F_{rel}	1 FIX	18.8 (11.9, 23.9)
Effect of MDR-1 (rs 29)	0.257 (0.0873, 0.427)	
σ_{prop} (CV%)	13.9 (9.62, 17.1)	

Table 1. Pharmacokinetic parameter estimates of the final model.

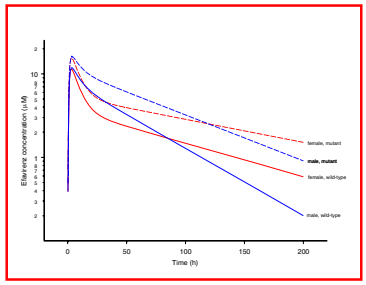

Figure 3. Simulated concentration-time profiles in four typical individuals.

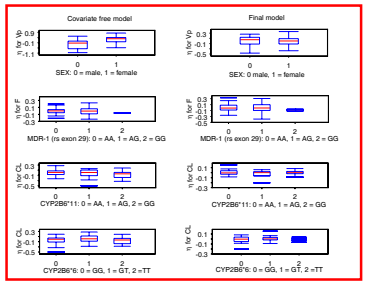

Figure 4. Relationship between covariates and between-subject variability for the covariate free and the final efavirenz model.

CONCLUSIONS

Efavirenz was observed to have an atypical absorption profile. A mixture of zero- and first-order sequential absorption could be interpreted as the result of dissolution rate limited absorption. The use of mixed effects modelling allowed the analysis and integration of multiple pharmacogenetic and demographic covariates in a pharmacokinetic/pharmacogenetic population model. The results indicate that CYP2B6 (516G>T and *11) as well as MDR-1 (rs exon 29) polymorphism and sex influence efvairenz pharmacokinetics. Presence of MDR-1 at absorptive and secretory sites explains its polymorphic effect on efavirenz bioavailability. The large peripheral volume of distribution observed in women could be due to a high body fat content in female subjects. Ultimately, to assess the clinical relevance upon efficacy, safety and individualized dosing strategies these covariate effects and pharmacogenetic polymorphisms should be investigated in patients under steady-state conditions.

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