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CYP2B6, *CYP2A6* and *UGT2B7* Genetic Polymorphisms are Predictors of Efavirenz Mid-dose Concentration in HIV-infected Patients

Awewura Kwara[a], **Margaret Lartey**[b], **Kwamena W.C. Sagoe**[b], **Ernest Kenu**[c], and **Michael H. Court**[d]

[a] Warren Alpert Medical School of Brown University and The Miriam Hospital, Providence, Rhode Island [b] University of Ghana Medical School, Accra, Ghana [c] Korle-Bu Teaching Hospital, Accra, Ghana [d] Tufts University School of Medicine and Tufts Medical Center, Boston, Massachusetts

Abstract

Objective—UDP-glucuronosyltransferase (UGT) 2B7 was recently identified as the main enzyme mediating efavirenz N-glucuronidation. In this study we determined whether selected *UGT2B7* polymorphisms could be used to enhance the prediction of efavirenz plasma concentrations from *CYP2B6* and *CYP2A6* genotypes.

Methods—Mid-dose efavirenz plasma concentrations were determined in 94 HIV-infected Ghanaian patients at 2–8 weeks of antiretroviral therapy. *CYP2B6* and *CYP2A6* genotypes had been previously reported. *UGT2B7* exon 2 SNPs c.735A>G (*UGT2B7**1c; rs28365062) and c.802C>T (H268Y; *UGT2B7**2; rs7439366) were determined by direct sequencing with *UGT2B7**1a defined as the reference allele. Relationships between efavirenz plasma concentrations, demographic variables and genotypes were evaluated by univariate and multivariate statistical approaches.

Results—The mean (±SD) mid-dose efavirenz plasma concentration was 3218 (±3905) ng/mL with coefficient of variation of 121%. Independent predictors of efavirenz concentration included *CYP2B6* c.516TT genotype (4,030 ng/mL increase; 95% CI, 2,882–5,505 ng/mL, $P<0.001$), *UGT2B7**1a* carrier status (475 ng/mL increase; 95% CI, 138–899 ng/mL, $P=0.004$) and *CYP2A6**9* and/or **17* carrier status (372 ng/mL increase; 95% CI, 74–742 ng/mL, $P=0.013$). Overall, *CYP2B6* c.516TT genotype, *UGT2B7**1a carrier status and *CYP2A6**9 or *17* carrier status accounted for 45.2%, 10.1%, and 8.6% of the total variance, respectively.

Conclusions—Our findings demonstrate independent effects of *CYP2A6* and *UGT2B7* genetic variation on efavirenz disposition beyond that of the *CYP2B6* polymorphisms. The development and testing of a pharmacogenetic algorithm for estimating the appropriate dose of efavirenz should incorporate genotypic data from both the oxidative and glucuronidation pathways.

Corresponding author: Awewura Kwara, MD, The Miriam Hospital, 164 Summit Avenue, Providence, RI 02906, USA, Telephone: 401 793-2463, Fax: 401 793-4704, akwara@lifespan.org.

Authors' contributions

Study concept and design: Kwara, Lartey, Court.
Conduct of study and acquisition of data: Lartey, Sagoe, Kenu, Kwara, Court.
Analysis and interpretation of data and drafting of manuscript: Kwara, Court
Critical revision of the manuscript for important intellectual content: All authors.
Review of the manuscript: All authors.

Keywords

CYP2B6; CYP2A6; UGT2B7; genetic polymorphisms; efavirenz concentration

Introduction

Efavirenz is an essential component of first-line antiretroviral regimen for HIV-infected patients [1,2], as well as the preferred third drug in patients with tuberculosis (TB) coinfection requiring rifampin-containing therapy [3,4]. The fixed-dose of 600 mg/day for adults is associated with significant inter-individual variability in plasma concentrations as well as clinical effects [5–7]. The variability in plasma concentrations appears to be even wider during co-administration with rifampin-containing TB therapy [8,9]. Mid-dose or trough efavirenz plasma concentrations below 1000 ng/mL has been associated with increased risk of virologic failure [6,7,10], while concentrations above 4000 ng/mL have been associated with risk of central nervous system side effects [6,7]. Although, this therapeutic range has not been validated by other investigators [11], the well-known substantial inter-individual variability (>100% coefficient of variation) in efavirenz plasma concentrations after fixed standard dosing has the potential to place some individuals at risk of supra- or sub-therapeutic concentrations.

Efavirenz is oxidized primarily by hepatic CYP2B6 to form 8-hydroxy and 7-hydroxy efavirenz, with minor contributions from CYP3A4/5 and CYP2A6 [12,13]. The *CYP2B6* gene is highly polymorphic and subject to pronounced inter-individual variability in expression and function [14]. It has also been shown that *CYP2A6* genetic variation may account for some of the unexplained variability in efavirenz plasma concentrations [15,16]. Efavirenz also undergoes direct conjugation to form an N-glucuronide [13,17]. UDP-glucuronosyltransferase (UGT) 2B7 was recently identified as the main UGT isoform responsible for the efavirenz glucuronidation [18]. In previous studies, we investigated the pharmacogenetics of efavirenz including effects of *CYP2B6* and *CYP2A6* polymorphisms in two cohorts of HIV-infected patients [16,19]. In this study, we have performed additional exploratory analyses to investigate the potential utility of *UGT2B7* genotyping as a means to improve the prediction of efavirenz plasma concentrations over that of the *CYP2B6* and *CYP2A6* genotypes alone.

METHODS

Study patients

The study included 94 HIV-infected Ghanaian patients who were enrolled between January 2004 and December 2007. The inclusion and exclusion criteria are previously published [16, 19]. HIV-infected patients with or without new TB coinfection, aged at least 18 years old, antiretroviral naïve and CD4 count ≤ 250 cell/μL were prospectively enrolled. Fifty-six patients (60%) had TB coinfection and 48 patients (51%) were receiving rifampin-containing therapy at pharmacokinetic sampling. All patients received efavirenz at 600 mg daily dose plus two nucleoside reverse transcriptase inhibitors. The studies were reviewed and approved by the Institutional Review Boards of the appropriate institutions. A signed informed consent was obtained from all patients prior to enrollment.

Pharmacokinetic sampling

Mid-dose blood samples obtained at weeks 4 and 8 of therapy in one group of 66 patients were included in these analyses. The mean efavirenz concentration at these two timed points was used in the final analysis. Up to the time of pharmacokinetic sampling, adherence as assessed by patient self-reports, pharmacy refill records and pill count was excellent in all except one patient who was not included in the analysis. Mid-dose sampling is frequently used in clinical

studies of efavirenz disposition for patient convenience since the drug is invariably taken at bedtime to minimize central nervous system side effects during the day [6,10]. In the second group of 28 patients, blood samples including a 12-hour sample after observed dosing were obtained at two weeks of antiretroviral therapy. Data from the two studies were combined in order to enhance the statistical power of the analyses. Multivariate analyses (described below) confirmed that the identified genotype associations were independent of the data source (cohort 1 or 2) thereby validating merging of the data sets.

Pharmacokinetic analysis

Efavirenz plasma concentrations were measured using a validated high-performance liquid chromatography (HPLC)/UV method [20]. The laboratory is CLIA certified, and participates in quarterly national and international external proficiency testing.

CYP2B6, CYP2A6 and UGT2B7 genotyping

Subjects were genotyped for *CYP2B6* c.516G>T (Q172H, rs3745274), c.983T>C (I328T, rs28399499), *CYP2A6 *9B*, (g.1836G>T, rs8192726), and *CYP2A6 *17* (g.5065G>A, c. 1093G>A, M365V, rs28399454) as previously described [16]. Genotypes for the *UGT2B7* exon 2 SNPs c.802C>T (H268Y; *UGT2B7**2; rs7439366) and c.735A>G (*UGT2B7**1c; rs28365062) were determined by genomic PCR amplification and sequencing as previously described with minor modifications [21,22]. In addition to *UGT2B7* c.802C>T (H268Y; *UGT2B7**2; rs7439366) being nonsynonymous (H268Y), c.735A>G (*UGT2B7**1c; rs28365062) was chosen for this analysis because they allowed discrimination of the 3 most common *UGT2B7* alleles that have been identified to date [23,24]. *UGT2B7**1a (reference), *UGT2B7**2, and *UGT2B7**1c alleles were inferred from the SNP genotype data according to the UGT Allele Nomenclature Committee recommendation (http://www.ugtalleles.ulaval.ca).

Statistical analysis

Statistical analyses were performed using Sigmaplot 11 software (Systat, San Jose, CA). Univariate analyses of effects of patient demographics and enzyme genotypes on efavirenz mid-dose concentrations were assessed by Mann-Whitney rank sum test or by linear regression. A forward stepwise multiple linear regression analysis was used construct a predictive model using patient demographic factors and genotypes as independent variables and $\log_{10}$ efavirenz concentrations as the dependent variable. Efavirenz concentration data was log-transformed to achieve data normality for the multiple regression analysis. A P value < 0.05 was considered significant.

Results

Study population

Of 94 patients, the mean (±SD) age was 39 (±8) years, body weight was 54 (±11) kilograms, and body mass index (BMI) was 19.3 (±3.9). Forty-four patients (47%) were female. The mean (±SD) mid-dose efavirenz plasma concentration was 3218 (±3905) ng/mL with coefficient of variation of 121%. Twenty-one patients (11 receiving rifampin) and nine patients (5 receiving rifampin) had efavirenz concentrations over 4000 ng/mL and under 1000 ng/mL, respectively.

Predictors of efavirenz concentration identified by univariate analysis

In the univariate analysis, only *CYP2B6* 516TT genotype as well as *CYP2A6**9, *CYP2A6**9* and/or **17*, *UGT2B7**1a and *2 carrier status were significantly associated with altered efavirenz plasma concentration (Table 1).

Independent predictors of efavirenz concentration identified by multiple linear regression

A forward stepwise multiple linear regression analysis was then performed to identify independent predictors of efavirenz concentration and estimate the contribution of each factor to pharmacokinetic variability. *CYP2B6* c.516TT genotype was the first variable to enter the model accounting for a 4,030 ng/mL increase (95% CI, 2,882–5,505 ng/mL, $P<0.001$) in efavirenz concentration. *UGT2B7*1a* carrier status was the second variable to enter the model associated with a 475 ng/mL (95% CI, 138–899 ng/mL, $P=0.004$) increase in efavirenz concentration. *CYP2A6*9* and/or **17* carrier status was the last variable to enter the model associated with 372 ng/mL increase (95% CI, 74–742 ng/mL, $P=0.013$). Other factors examined including *CYP2B6* 516GG genotype, *CYP2B6* 983TC genotype, *CYP2B6*9* carrier status, *CYP2B6*17* carrier status, *UGT2B7*1c* carrier status, *UGT2B7*2* carrier status, rifampin co-administration, age, sex, alcohol use, body weight and BMI were not significantly associated with $\log_{10}$ efavirenz concentration. The final linear regression model was:

$$\text{Predicted } \log_{10}[\text{EFV}]\,(\text{ng/mL}) = 3.068 + (0.648 \times \textit{CYP2B6}\,\text{c.516TT}) + (0.148 \times \textit{UGT2B7}^{*}1\text{a}) + (0.120 \times \textit{CYP2A6}^{*}9\text{or}^{*}17)$$

Where [EFV] is efavirenz concentration (in ng/mL), *CYP2B6* c.516TT genotype (0=GG/GT, 1=TT), *UGT2B7**1a carrier status (0=*1a non-carrier, 1=*1a carrier), *CYP2A6*9* or **17* (0=*9 or *17 non-carrier, 1=*9 or *17 carrier). The coefficient of determination (R^2) from the regression analysis was 0.652 ($P<0.001$) indicating that 65.2% of the total variance was explained by the model. *CYP2B6* c.516TT genotype, *UGT2B7**1a carrier status and *CYP2A6*9* or **17* carrier status and accounted for 45.2%, 10.1%, and 8.6% of the total variance, respectively.

Gene-gene interactions

It has been proposed that the alternate pathways for efavirenz metabolism (mediated by CYP2A6 or UGT2B7) might only be of importance in individuals with impaired CYP2B6 metabolism [15] (i.e. those with *CYP2B6* c.516TT genotype). Consequently we also assessed the possibility of such gene-gene interactions by inclusion of several gene-gene interaction terms (*CYP2B6* c.516TT genotype x *UGT2B7**1a carrier status and CYP2B6 c.516TT genotype x *CYP2A6*9 or *17* variant status) in our multiple linear regression model. However, we could not detect any statistically significant interactions between *CYP2B6* c.516TT genotype and *UGT2B7**1a carrier status (P=0.325), or between CYP2B6 c.516TT genotype and *CYP2A6*9 or *17* variant status (P=0.605) using this approach.

Discussion

The results of this study identify *UGT2B7* genetic polymorphism (specifically the *UGT2B7**1a allele) as an additional independent predictor of efavirenz plasma concentration beyond that provided by the well studied *CYP2B6* c.516G>T polymorphism [25] and the recently identified contribution of several *CYP2A6* variants [15,16]. Importantly, our findings provide the first *in vivo* evidence supporting a role for UGT2B7 in the metabolism of efavirenz by showing a significant relationship between efavirenz plasma concentrations and *UGT2B7* genetic variation.

Consistent with previous reports [19,26–30], the *CYP2B6* 516G>T SNP was by far the key determinant of inter-individual variability in efavirenz plasma concentrations in our cohorts, and the effect was observed irrespective of rifampin co-administration. Based on multiple linear regression analysis the *CYP2B6* 516G>T SNP accounted for as much as 45% of the observed variability in efavirenz concentrations with the *UGT2B7**1a allele accounting for a further 10% of variability, and the *CYP2A6* slow metabolizing variants explaining another 9%

of variability. The resultant regression model also indicates that the presence of the *CYP2B6* 516TT genotype is associated with an average 345% higher efavirenz concentration with smaller but statistically significant effects from the *UGT2B7**1a allele (41% higher efavirenz concentrations) and *CYP2A6* slow metabolizing variants (32% higher efavirenz concentrations). The current discoveries of genetic variants associated with altered efavirenz levels in the alternate pathways of efavirenz metabolism have the potential to improve the ability to identify patients who could be treated with effectively reduced or increase efavirenz dose through predictive genetic testing.

We observed over 120% variability in the mid-dose efavirenz plasma concentration in our patients with 32% of them having concentrations outside the presumed therapeutic range. Although the utility of pharmacogenetic data to predict treatment failure with efavirenz is not well studied, *CYP2B6* c.516TT genotype has been associated with a higher frequency of CNS side effects [27,31]. Severe CNS toxicities associated with supra-therapeutic efavirenz concentrations has also been reported in individual with *CYP2B6* 516TT genotype, most of whom benefited from dose reduction to 200 mg daily, while others required discontinuation of efavirenz [32–34]. In contrast, higher efavirenz doses up to 1600 mg daily were required to achieve desired plasma concentrations, as well as virologic suppression in two patients with no identifiable slow-metabolizing phenotype mutation who were also treated rifampin [35]. Taken together, there may be a role for tailored dosing in some patients and this can be improved by pharmacogenetic prediction of individual's likelihood to have concentrations outside the therapeutic range.

The main limitation of our study is the somewhat limited number of *CYP2B6*, *CYP2A6* and *UGT2B7* SNPs studied as rarer functional SNPs might impact efavirenz clearance. We also did not evaluate the possible contribution of *CYP3A4/5* genetic variation to efavirenz concentrations. However, the multivariate modeling suggested that over 60% of the variability in efavirenz concentrations in our population was explained by our genetic data. Antiretroviral therapy is currently a life-long undertaken and optimization of drug regimens will reduce the chances of undesired outcomes such as toxicities or virologic failure. In African populations, *CYP2B6* 516TT genotype is common and a priori dose reduction based on genetic testing has been proposed to reduce cost and minimize toxicities [28]. Accurate identification of outliers who would benefit from efavirenz dose adjustment at the population level would require a strategy that includes maximized prediction of drug exposure based clinical and genetic factors using a combination of genetic factors [36]. Our findings demonstrate independent effects of *CYP2A6*, and *UGT2B7* genetic variation on efavirenz disposition beyond that due to *CYP2B6* polymorphisms. The development and testing of a pharmacogenetic algorithm for estimating the appropriate dose of efavirenz should incorporate genotypic data from both the oxidative and glucuronidation pathways.

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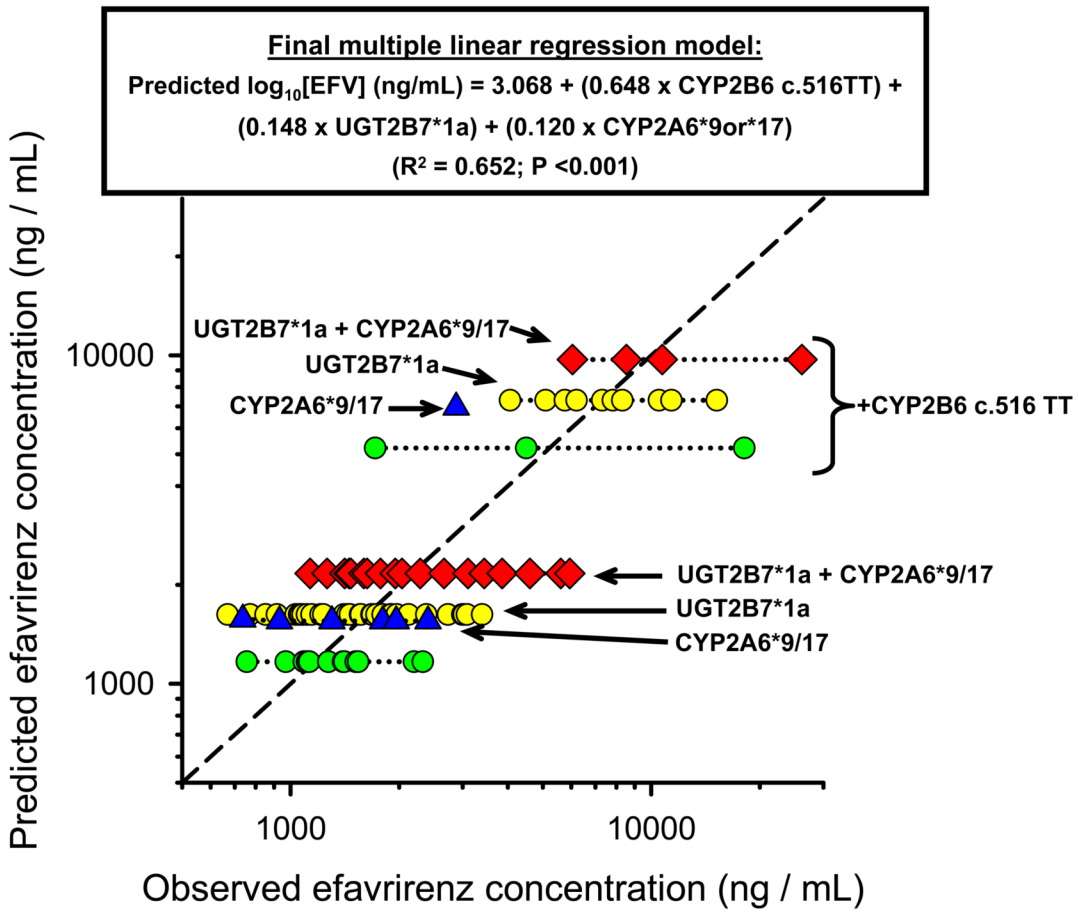

Fig. 1.

Scatter plot showing the relationship between pharmacogenetic-predicted efavirenz mid-dose plasma concentrations (y-axis) and observed concentration (x-axis) in 94 HIV-infected patients. Log_{10} efavirenz mid-dose plasma concentrations predictions for each subject were made based on their genotype carrier status (CYP2B6 c.516TT, CYP2A6*9 or *17 and/or UGT2B7*1a as indicated by arrows) using the pharmacogenetic algorithm derived by multiple linear regression analysis (model and associated goodness of fit statistics are shown at the top of graph). Log_{10} efavirenz concentration units are back-transformed into linear units for presentation in the plot.

Table 1

Predictors of mid-dose efavirenz plasma concentration assessed by univariate analysis

	Efavirenz concentration (ng/mL)		
Variable	**Median**	**IQR**	***P* value**
Age[a]	---	---	0.719
Weight[a]	---	---	0.199
BMI[a]	---	---	0.055
Gender			0.542
F (n = 44)	1641	1252 – 2980	
M (n = 50)	1752	1281 – 4058	
History of alcohol use			0.045
No (n = 67)	1597	1239 – 2714	
Yes (n = 27)	2325	1441 – 5481	
Concurrent rifampin			0.266
No (n = 48)	1582	1272 – 2731	
Yes (n = 46)	2493	1283 – 4281	
CYP2B6 c.516 TT genotype			**< 0.001**
GG/GT (n = 76)	1528	1138 – 2161	
TT (n = 18)	7568	5092 – 10726	
CYP2B6 c.983 TC genotype			0.346
TT (n = 86)	1681	1262 – 3397	
TC (n = 8)	2515	1795 – 3271	
*CYP2A6*9*			**0.028**
Non-carrier (n = 83)	1597	1216 – 3013	
Carrier (n = 11)	3102	1820 – 4521	
*CYP2A6*17*			0.509
Non-carrier (n = 71)	1685	1216 – 3097	
Carrier (n = 23)	1950	1347 – 4129	
*CYP2A6*9* and/or **17*			**0.044**
Non-carrier (n = 62)	1560	1126 – 2993	
Carrier (n = 32)	2162	1460 – 4244	
*UGT2B7**1a			**0.021**
Non-carrier (n = 64)[b]	1408	1111 – 2140	
Carrier (n = 23)[b]	1925	1421 – 4332	
*UGT2B7**1c			0.310
Non-carrier (n = 64)[b]	1773	1004 – 3645	
Carrier (n = 23)[b]	1766	1393 – 3250	
*UGT2B7**2			**0.020**
Non-carrier (n = 40)[b]	2306	1436 – 5903	
Carrier (n = 47)[b]	1562	1240 – 2334	

[a] Relationship between continuous variables and $\log_{10}$ mid-dose efavirenz plasma concentration were assessed by linear regression. All other variables were assessed by Student's t-test.

[b] PCR amplification of UGT2B7 exon 2 was not successful in 7 of 94 patients.