

CYP2B6: Explaining Efavirenz Pharmacokinetics

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The relatively “new” isoenzyme CYP2B6 is characterized by wide interindividual variability in hepatic expression and activity. Recent pharmacogenetic studies suggest that CYP2B6 is highly polymorphic and that genetic variants are of great importance for efavirenz pharmacokinetics.

GENERAL ASPECTS OF CYP2B6

Cytochrome P450 2B6 (CYP2B6) was described by Yamano *et al* in 1989 [1]. CYP2B6 is expressed in liver and to a lesser extent in other tissues including uterine endometrium, peripheral blood leukocytes, respiratory tract, kidney, small intestine, brain and skin [2-5]. The human *CYP2B6* gene, together with one pseudogene (*CYP2B7*), integrate a cluster of the *CYP2* family (*CYP2A*, *CYP2B* and *CYP2F*) on chromosome 19 [6].

The importance of CYP2B6 has been underestimated in the past because of reported low levels of liver expression [7], and its unrecognized role in drug metabolism. However CYP2B6 currently represents ~6% of the total liver CYP P-450 content [8], and it is involved in the metabolism of important therapeutic drugs such as bupropion, cyclophosphamide and tamoxifen [2]. In addition, CYP2B6 is induced by clotrimazole, phenobarbital, rifampin, phenytoin and ritonavir, and is inhibited by clopidogrel, ticlopidine, thiotepa and 17- α -ethynylestradiol. Induction and inhibition of CYP2B6 is of clinical relevance due to potential drug-drug interactions [9-13]. CYP2B6 is important in antiretroviral therapy since it is the main isoenzyme responsible for the metabolism of efavirenz (EFV).

EFAVIRENZ PHARMACOKINETICS

EFV is metabolized by CYP2B6 and to a lesser extent CYP3A4 [14-16]. Three EFV metabolites have been identified: 8-hydroxyefavirenz (major), 7-hydroxyefavirenz (minor), and a 8,14-dihydroxyefavirenz (secondary metabolite) [16, 17]. EFV pharmacokinetics is characterized by marked interindividual variability in plasma levels [18]. This variability was not found to be influenced by gender, however ethnic-related effects have been observed, thus raising the possibility that genetic factors might play a role [19].

PHARMACOGENETICS OF CYP2B6

CYP2B6 is characterized by wide interindividual variability in hepatic expression and catalytic activity, which is partly due to genetic polymorphisms [20, 21]. Recent studies have reported numerous CYP2B6 variants, thus underscoring that this isoenzyme is highly polymorphic [22-27] (CYPAllele nomenclature homepage, <http://www.cypalleles.ki.se>) (Figure 1). In addition, our laboratory has identified the occurrence of partial gene deletion by unequal cross-over between human *CYP2B6* and their pseudogene *CYP2B7* leading to a functionally impaired hybrid allele (Rotger *et al submitted*).

Studies have mostly focused on the diminished-function allele *6 [Q172H, K262R], since this allele is present at high frequencies in different populations, i.e. ~ 15% in Asians up to ~ 50% in Blacks [23]. The effect of the *6 allele has been clearly correlated to high EFV plasma levels [28-31]. Although, the reason for this is not clear since experimental results are somewhat contradictory. Reports with human liver microsomes revealed lower apoprotein expression among *6 carriers [20, 22, 32] as well as decreased activity when using S-mephenytoin as a substrate [20]. However, increased activity was observed when using cyclophosphamide [32]. Increased *in vitro* activity was also reported using 7-ethoxy-4-trifluoromethylcoumarin or 7-ethoxycoumarin substrates [33, 34]. In contrast, we reported a 70% loss in activity when using bupropion as the substrate [35]. *In vivo* studies with bupropion suggest that the *6 allele contributes to lower activity [36, 37]. In contrast, another SNP, c.1459C>T [R487C] in allele *5, which has been associated with reduced expression in human liver microsomes [20, 24], does not affect EFV pharmacokinetics [28, 30, 35, 38]. New loss-of-function alleles such as *16, *18, *27 and *28 have been associated with high EFV plasma levels [26, 35].

Two alleles are associated with increased function. SNP c.785A>G [K262R] in allele *4 has an increased activity *in vitro* towards 7-ethoxy-4-trifluoromethylcoumarin and bupropion, but a decreased activity towards benzphetamine [34, 39]. We observed a trend for lower EFV plasma levels in *1/*4 heterozygotes versus *1/*1 carriers [35], which is in agreement with previous *in vivo* reports for bupropion [40]. The -82T>C promoter variant, which

characterizes the allele *22, is associated with enhanced transcription as well as increased expression/activity of the protein [27]. More research is needed to characterize increased function alleles, as non-adherence to treatment confounds clinical studies of EFV pharmacokinetics.

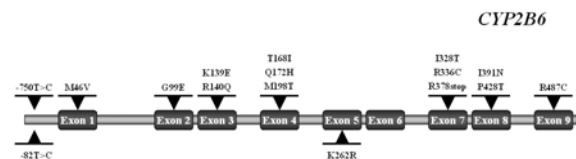


Figure 1: CYP2B6 functional polymorphisms. Loss/diminished-function polymorphisms are indicated in upper part of the figure. Gain-of-function polymorphisms are indicated in the lower part of the figure.

EFV PHARMACOKINETICS AND CYP2B6 POLYMORPHISMS

CYP2B6 genotyping may identify individuals who are at risk of unexpectedly high EFV plasma levels. Individuals homozygous for a loss/diminished-function allele have a likelihood ratio of 35 of presenting very high EFV plasma levels. In contrast, EFV plasma levels in heterozygous individuals may be in the therapeutic range, as they still have enough functional enzyme to metabolize the drug [35]. Although genotyping exclusively for *6 allele will identify a significant proportion of individuals at risk of unexpectedly high EFV plasma levels, our recent study shows that predictive value of *CYP2B6* genotyping is significantly enhanced by including the less common loss/diminished-function alleles into the analysis [35].

EFV PHARMACODYNAMICS AND CYP2B6 POLYMORPHISMS

The most frequently reported adverse effect for EFV-containing therapy is neuropsychological toxicity which may affect up to 50% of individuals [41]. Symptoms usually resolve within the first month of therapy [42]; however, neuropsychological toxicity may occur with long term therapy [43, 44]. Two studies explored the effect of *CYP2B6* polymorphisms in EFV neuropsychological toxicity. Haas *et al* reported an association of *6 allele with toxicity at week 1 of therapy [28]. The Swiss HIV Cohort Study reported an association of *6 allele and long term toxicity [31]. There is no clear association between *CYP2B6* genotype and treatment success [45]. In contrast, genetic interaction models that include variants in multiple metabolic or transport genes propose a gene-gene interaction between *ABCB1* 2677G>T and *CYP2B6* 516G>T that predicts virologic failure [46]. We have recently described a possible *drug-drug-gene* interaction, i.e. a

pharmacokinetic interaction between tenofovir and EFV restricted to poor *CYP2B6*-metabolisers [47].

CONCLUSIONS

CYP2B6 genetic variation explains to a great extent EFV pharmacokinetics. However, EFV pharmacodynamics studies suggest that additional factors, yet to be identified, are also implicated. Future studies should specifically address this question.

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