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Paradoxically Elevated Efavirenz Concentrations in HIV/TB Co-infected Patients with *CYP2B6* 516TT Genotype on Rifampin-containing Antituberculous Therapy

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Summary

Some individuals have higher efavirenz plasma concentrations during rifampin-containing tuberculosis (TB) therapy, contrary to the expected induction effect of rifampin. Among HIV-infected patients without (N=38) and with TB on rifampin-containing therapy (N=18), we tested the hypothesis that drug-gene interaction may explain the highly variable drug interactions. Two-way analysis of variance revealed a significant interaction between *CYP2B6* 516G→T polymorphism and rifampin-containing therapy, suggesting that efavirenz dose-adjustment may need to be individualized based on the patient's genotype.

Keywords

CYP2B6 polymorphism; drug-gene interaction; rifampin; efavirenz concentration

Efavirenz-based antiretroviral regimen is preferred during rifampin-containing antituberculous therapy. The adult fixed-dose of 600 mg/day is associated with wide inter-individual variability in plasma concentrations as well as clinical outcome [1–3]. The variability in efavirenz concentrations is even greater during coadministration with rifampin or rifampin-containing antituberculous therapy [4–6], suggesting a variable degree of drug-drug interaction. Among healthy volunteers, rifampin caused a significant reduction in efavirenz area under the curve (AUC) in 10 subjects but two subjects had higher AUC on than off rifampin [4]. In HIV/TB co-infected patients, the change in efavirenz AUC with concomitant rifampin administration ranged from –65% to +37% in one study [7]. Efavirenz is primarily metabolized by hepatic *CYP2B6*, with some contributions from *CYP3A4/5* [8], *CYP2A6*[9] and *UGT2B7* enzymes [10]. The lack of induction of efavirenz metabolism by

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Conflict of Interest:

Dr Kwara has previously received a research grant not related to this study from Bristol Myer-Squibb. Drs Lartey, Court, and Mr Sagoe report no conflict of interest.

rifampin in some individuals is contrary to the expected effect of rifampin on CYP2B6 activity [11].

A bimodal effect of rifampin-containing therapy on efavirenz plasma concentrations has also been reported, with paradoxically higher concentrations with antituberculous therapy in the patients who appeared to be slow efavirenz metabolizers (based on phenotype only since enzyme genotyping was not done) [5, 12]. Also, some HIV/TB co-infected patients have required decreased efavirenz doses and/or discontinuation during rifampin-containing therapy because of severe toxicities associated with elevated efavirenz concentrations [13, 14].

Elevations of efavirenz plasma concentration with rifampin-containing therapy that occur predominantly in persons with slow metabolizing phenotype suggest the possibility of a genotype-dependent drug-drug interaction. In this study we investigated the potential for such an interaction between rifampin-containing antituberculous therapy and *CYP2B6* 516 G→T polymorphism using data from a pharmacokinetic study conducted previously. The characteristics of the patients and results of the primary analysis are reported elsewhere [15]. All patients received efavirenz 600 mg/day with didanosine and lamivudine, and pharmacokinetic sampling performed on day-28 of therapy. Antiretroviral therapy was initiated within 2–8 weeks of antituberculous therapy in co-infected patients and only those on concurrent therapy at the time of pharmacokinetic sampling were included in this analysis. The study was approved by the Institutional Review Board of the Nogouchi Memorial Institute for Medical Research, Ghana. Informed written consent was obtained from all patients.

Pharmacokinetic samples were drawn at approximately 12 hours after the efavirenz dose was taken. Efavirenz plasma concentrations were measured using a validated high-performance liquid chromatography (HPLC)/UV method [16]. Subjects were genotyped for *CYP2B6* c.516G→T (Q172H, rs3745274) nucleic acid genotyping assay (Applied Biosystems, Foster City, CA). Two-way analysis of variance (ANOVA), which incorporates an interaction model, was used to investigate effects of *CYP2B6* 516G→T genotype and rifampin-containing TB therapy. As in previous studies [15, 17], concentration data were not normally distributed and so they were log transformed prior to analysis. In instances where the ANOVA indicated a significant effect ($P < 0.05$), post-hoc multiple pair-wise comparison testing was performed using the Student-Newman-Keuls method to identify groups which were significantly different from each other.

The analysis included 38 HIV-infected patients on efavirenz-based therapy and 18 HIV/TB co-infected patients on efavirenz-based and rifampin-containing antituberculous therapies. Concentration data from individual subjects categorized by *CYP2B6* 516G→T genotype and type of therapy are shown in Fig. 1. The two-way ANOVA revealed a statistically significant effect of *CYP2B6* 516 genotype on efavirenz plasma concentrations as well as an interaction between *CYP2B6* 516G→T genotype and the antituberculous therapy ($P < 0.001$ for *CYP2B6* 516G→T genotype; $P = 0.089$ for rifampin-containing therapy; $P = 0.022$ for interaction). *Post hoc* pairwise analysis showed that patients with *CYP2B6* 516TT genotype who were receiving concurrent therapy had a significantly higher geometric mean efavirenz

concentration than those on only antiretroviral therapy (14689 vs. 6012 ng/mL, respectively; $P=0.006$) (Fig. 1). Patients with 516GT genotype on concurrent antituberculous therapy had a slightly higher geometric mean efavirenz concentration than those on HAART only (1901 vs. 1778 ng/mL) and the patients with the 516GG genotype on antituberculous therapy had a lower geometric mean efavirenz concentrations than those with the 516GG genotype on HAART only (1291 vs. 1552 ng/mL) but these latter differences between therapeutic groups did not achieve statistical significance ($P>0.05$).

As a CYP2B6 enzyme inducer, rifampin co-administration would be expected to enhance efavirenz clearance and reduce plasma levels. However, in this study we found that the patients with *CYP2B6* 516TT genotype and receiving concomitant antituberculous therapy had higher efavirenz plasma concentrations than those subjects with the same genotype but not receiving antituberculous therapy. These findings are consistent with previous reports of elevated efavirenz concentration with rifampin-containing antituberculous therapy in HIV/TB co-infected patients who appeared to have slow metabolizing phenotype as genotyping was not done [5, 12, 14]. The paradoxical effect of antituberculous therapy in this study may be due to increased susceptibility of the CYP2B6 (172-histidine) variant allozyme (resulting from the c.516G→T polymorphism) to inhibition by one (or more) of the antituberculous drugs as compared with the reference CYP2B6 (172-glutamine) enzyme. Alternately, efavirenz metabolism may be inhibited by effects on the (non-CYP2B6) accessory pathways leading to higher efavirenz concentrations. CYP2A6 mediated 7-hydroxylation is identified as an important alternate pathway in the metabolism of efavirenz [18] and may be the major pathway for efavirenz clearance in *CYP2B6* slow metabolizers [19]. Thus, inhibition of CYP2A6 by one (or more) of the antituberculous drugs could explain the higher concentrations. Studies are needed to determine the mechanism by which addition of the standard four-drug antituberculous therapy causes higher efavirenz concentrations in *CYP2B6* slow metabolizers.

Our study has some limitations. Firstly, the sample size is small and the lack of significant effect of antituberculous therapy on efavirenz concentrations in the 516GG and GT genotype groups should be interpreted with caution. Secondly, the study compares two different patient populations and the differences seen in the 516TT genotype group could be due to population differences. However, our observation is supported by previous studies that showed paradoxically higher efavirenz concentrations during antituberculous therapy in the patients who appeared to be slow efavirenz metabolizers [5, 12]. If our results are confirmed in larger studies, CYP2B6 genotyping could inform rational decisions about efavirenz dosing or alternate therapy in HIV/TB co-infected patients.

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Fig. 1.

Influence of *CYP2B6* c.516G>T genotypes and rifampin-containing antituberculous therapy on efavirenz plasma mid-dose concentrations. There was a significant interaction between *CYP2B6* G→T polymorphism and rifampin-containing therapy ($P = 0.022$; 2-way ANOVA). Shown are the P values from the post-hoc multiple pair-wise comparisons (Student-Newman-Kuels test) within each genotype group. The horizontal bars represent the geometric mean efavirenz concentration of each genotype group.