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Rifampin enhances cytochrome P450 (CYP) 2B6-mediated efavirenz 8-hydroxylation in healthy volunteers

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ABSTRACT

The effect of rifampin on the *in vivo* metabolism of the antiretroviral drug efavirenz was evaluated in healthy volunteers. In a cross-over placebo control trial, healthy subjects ($n = 20$) were administered a single 600 mg oral dose of efavirenz after pretreatment with placebo or rifampin (600 mg/day for 10 days). Plasma and urine concentrations of efavirenz, 8-hydroxyefavirenz and 8,14-dihydroxyefavirenz were measured by LC–MS/MS. Compared to placebo treatment, rifampin increased the oral clearance (by ~2.5-fold) and decreased maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve ($AUC_{0-\infty}$) of efavirenz (by ~1.6- and ~2.5-fold respectively) ($p < 0.001$). Rifampin treatment substantially increased the C_{max} and AUC_{0-12h} of 8-hydroxyefavirenz and 8,14-di hydroxyefavirenz, metabolic ratio (AUC_{0-72h} of metabolites to AUC_{0-72h} efavirenz) and the amount of metabolites excreted in urine (Ae_{0-12hr}) (all, $p < 0.01$). Female subjects had longer elimination half-life (1.6–2.2-fold) and larger weight-adjusted distribution volume (1.6–1.9-fold) of efavirenz than male subjects ($p < 0.05$) in placebo and rifampin treated groups respectively. In conclusion, rifampin enhances CYP2B6-mediated efavirenz 8-hydroxylation *in vivo*. The metabolism of a single oral dose of efavirenz may be a suitable *in vivo* marker of CYP2B6 activity to evaluate induction drug interactions involving this enzyme.
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1. Introduction

The cytochrome P450 (CYP) 2B6 represents on average ~3–5% of the total hepatic P450 protein content and plays a more important role than previously estimated in the detoxification or activation of a growing list of clinically important drugs, endogenous compounds, and other compound of toxicological relevance, including procarcinogens and environmental toxicants (reviewed in and references therein: [1–6]). The protein expression and activity of CYP2B6 are highly variable among human livers *in vitro*, in part due to CYP2B6 genetic variation, with distinct ethnic and racial frequencies [7,8], and exposure to structurally diverse inducer [3] or inhibitor drugs [5,6,9]. This variability likely reflects large changes in activity *in vivo*. Indeed, emerging evidence link altered CYP2B6 metabolic status with clearance and/or pharmacodynamics effect of CYP2B6 substrates (e.g., efavirenz, methadone, ketamine, bupropion, propofol, cyclophosphamide, and nevirapine) [5–7].

Until recently, most studies addressing CYP2B6 regulation and function largely relied on data derived from *in vitro* models. Progress towards quantitative determination and prediction of the *in vivo* consequences of the wealth of *in vitro* data has been greatly hampered by the lack of selective and easy to use clinical phenotyping probe. Bupropion 4-hydroxylation, a reaction exclusively catalyzed by CYP2B6 [10], has been frequently used to assess the impact of genetic and nongenetic factors on CYP2B6 activity [9].

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However, the utility of bupropion in assessing *in vivo* induction drug interactions mediated by CYP2B6 [11] and functional consequences of *CYP2B6* genetic variants [12] appear to be limited. The significant contributions of non-CYP-mediated pathways [13], the involvement of CYPs other than CYP2B6 in bupropion metabolism [14], and the complex pharmacokinetic properties of bupropion and 4-hydroxybupropion [11,15] appear to be a major hindrance towards the use of bupropion metabolism as a probe of CYP2B6 activity. Although analysis of individual diastereomers of 4-hydroxybupropion has been suggested to improve the use of bupropion as *in vivo* probe of CYP2B6 activity [15], analytical and sample preparation challenges may hinder routine use of this approach. Thus, the search for a better *in vivo* probe of CYP2B6 activity continues.

Our group has demonstrated that CYP2B6 is the principal enzyme responsible for the *in vitro* metabolism of the antiretroviral drug efavirenz to 8-hydroxyefavirenz and then to dihydroxylated metabolite [16–18]. Efavirenz 8-hydroxylation, which accounts for over 80% of the overall *in vivo* metabolism of efavirenz in humans [19], is the main clearance mechanism for efavirenz. A strong association between *CYP2B6* genetic variants and efavirenz exposure was first reported in 2004 in HIV patients [20,21] and subsequent studies have repeatedly demonstrated the key role of CYP2B6 genetic variation not only in efavirenz metabolism but also in its pharmacological effects [5–7]. Available evidence suggests that efavirenz may be superior to bupropion or any other CYP2B6 substrates as an *in vivo* probe of CYP2B6 activity. However, although efavirenz has been recommended by the US Food and Drug Administration [22] and the European Medicines Agency [23] as an *in vivo* probe of CYP2B6, formal validation and the conditions of its use are lacking.

The *CYP2B6* gene is highly inducible by several structurally diverse compounds [3]. Rifampin, corner stone drug for the treatment of tuberculosis (TB), is one of the potent inducers of CYP2B6 *in vitro* [24,25] and enhances the elimination of known CYP2B6 substrates such as methadone [26], ketamine [27] and bupropion [15]. Based on this evidence and the fact that efavirenz is predominantly cleared by CYP2B6, rifampin is expected to enhance efavirenz elimination through induction of CYP2B6. However, numerous steady-state rifampin–efavirenz interaction studies conducted in HIV and TB co-infected patients have provided conflicting results regarding the effect of rifampin on efavirenz exposure: marginal decrease [28], no significant effect (most studies) (e.g. [29,30]), or a paradoxical increase in efavirenz exposure (e.g. [31]). Several factors may have contributed to these findings. Efavirenz induces its own metabolism (autoinduction) upon repeated administration through upregulation of CYP2B6 [32], which may mask the full induction potential of rifampin on steady-state efavirenz metabolism. To specifically assess the usefulness of efavirenz as an *in vivo* probe of CYP2B6 activity and to quantify induction potential of rifampin on CYP2B6, assessment should be performed at condition that shows no efavirenz autoinduction of metabolism, i.e., using a single dose of efavirenz. Such studies should first be established in healthy volunteers under controlled conditions as the effect of disease and the likelihood of polypharmacy prescription may confound rifampin–efavirenz interactions in HIV/TB co-infected patients. In addition, since sex-dependent differences may affect CYP2B6 activity at baseline and/or after induction with rifampin considering that CYP2B6 expression is up-regulated by female sex hormones (e.g., estradiol) [33] and that sex-dependent differences in rifampin exposure have been noted [34], it would be important to test whether CYP2B6 activity or rifampin–efavirenz interaction is different in male and female subjects.

In this randomized cross-over trial in healthy volunteers, the metabolism and pharmacokinetics of a single 600 mg oral dose of efavirenz alone and after chronic exposure to rifampin were determined. The objectives were to: determine the effect of rifampin on CYP2B6 activity *in vivo;* assess whether the metabolism of a single oral dose of efavirenz is a selective marker of CYP2B6 activity *in vivo* and quantitatively captures rifampin-mediated induction of this enzyme; identify pharmacokinetic indices of efavirenz that may serve as a better and easy to use marker of CYP2B6 activity; and assess whether CYP2B6 activity is different among male and female volunteers.

2. Methods

2.1. Study subjects

A total of 20 healthy volunteers (10 male and 10 female; 18–48 years old) participated in this study. The study protocol was approved by the Institutional Review Board (IRB#0302-01) of the Indiana University School of Medicine, Indianapolis, IN, USA. Signed and dated written informed consent form was obtained from each volunteer. Subjects were ascertained to be healthy by physical examination, standard clinical laboratory tests and medical histories. Subjects were required to abstain from taking any prescription drugs, over-the-counter medications, grapefruit or grapefruit juice, alcohol and caffeine containing beverages for 2 weeks before and during the entire study periods.

2.2. Study design

The study was a randomized, double blind placebo controlled cross-over trial. Eligible subjects were randomized to take either a daily 600 mg oral dose of rifampin or placebo pills starting day 1 through day 10. Riboflavin, which produces similar urine color as rifampin, was used as placebo. Riboflavin powder was purchased from local pharmacy in Indianapolis and packaged into red pills similar to those of rifampin oral pills. On day 11, pre-dose blood was collected and then subjects were administered a single 600 mg oral dose of efavirenz along with an additional dose (600 mg) of rifampin or placebo pills on an empty stomach with water. Blood samples were collected at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48 and 72 h after efavirenz dosing for pharmacokinetic analysis. Urine was collected at baseline and 0–12 h after efavirenz dosing and aliquot urine was saved after recording total urine volume.

After a wash-out period of 11 days, subjects started taking rifampin or placebo pills in a crossover fashion for 10 consecutive days and underwent the same procedure as in the first phase of the study. Plasma samples were separated by centrifugation for 20 min at 3000 rpm within an hour of blood collection. Plasma and urine samples were stored at −80 °C until analysis.

2.3. Quantification of drugs and metabolites

2.3.1. Chemicals

Efavirenz, 8-hydroxyefavirenz, nevirapine, ritonavir, rifampin and 25-desacetylrifampin were purchased from Toronto Research Chemicals Inc. (North York, Canada). β-Glucuronidase (Type H-2, from Helix pomatia) was purchased from Sigma–Aldrich (St. Louis, MO, USA). All the other chemicals and solvents were of the highest analytical grade available.

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