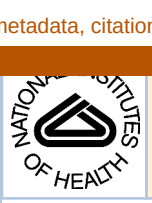

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The Influence of *CYP3A5* Genotype on Dexamethasone Induction of CYP3A Activity in African Americans

Patrick J. Roberts, **Kristan D. Rollins**, **Angela D. M. Kashuba**, **Mary F. Paine**, **Andrew C. Nelsen**, **Eric E. Williams**, **Cassandra Moran**, **Jatinder K Lamba**, **Erin G. Schuetz**, and **Roy L. Hawke**

Division of Pharmacotherapy & Experimental Therapeutics (PJR, KDR, ADMK, MFP, CAN, EEW, RLH), Department of Pediatrics, Division of Pediatric Hematology Oncology (CM), University of North Carolina, Chapel Hill, NC, USA; North Carolina Collaborative Pediatric Pharmacology Research Unit (CM), Duke University Medical Center and University of North Carolina, Chapel Hill, NC, USA; Department of Pharmaceutical Sciences (JKL, EGS), St Jude Children's Research Hospital, Memphis, TN, USA.

Abstract

The *CYP3A5*1* allele has been associated with differences in the metabolism of some CYP3A substrates. *CYP3A5* polymorphism may also influence susceptibility for certain drug interactions. We have previously noted a correlation between basal CYP3A activity and the inductive effects of dexamethasone using the erythromycin breath test (ERBT). To determine if *CYP3A5* polymorphism influences induction of CYP3A activity, we examined the effect of an anti-emetic regimen of dexamethasone, and the prototypical inducer rifampin, on the ERBT in a African American volunteers prospectively stratified by *CYP3A5*1* allele carrier-status. Mean basal ERBTs were significantly higher in *CYP3A5*1* carriers (2.71% ± 0.53%) versus non-carriers (2.12% ± 0.37%, P = 0.006). Rifampin increased ERBTs in *CYP3A5*1* carriers (4.68% vs 2.60%, P = 0.0008) and non-carriers (3.55% vs 2.11%, P = 0.0017), while dexamethasone increased ERBTs only in *CYP3A5*1* non-carriers (3.03% vs 2.14%, P = 0.031). *CYP3A5* polymorphism appears to influence susceptibility to induction-type drug interactions for some inducers, and *CYP3A5*1* non-carriers may be more susceptible to the inductive effects of dexamethasone due to lower basal CYP3A activity.

INTRODUCTION

Members of the cytochrome P450 3A (CYP3A) subfamily of drug metabolizing enzymes are the most abundantly expressed cytochrome P450 enzymes in human liver and are involved in the metabolism of nearly 50% of clinically used drugs (Wilkinson, 2005).

In adults, hepatic CYP3A activity reflects primarily the net contributions of CYP3A4 and CYP3A5 which share overlapping substrate specificities but differ with regard to tissue expression and transcriptional regulation (Gibson et al., 2002; Goodwin et al., 2002; Burk and Wojnowski, 2004). Recent efforts to understand inter-individual variability in CYP3A activity have focused primarily on *CYP3A5* polymorphisms since variability in the contribution of functional CYP3A5 activity could influence an individual's susceptibility to inducer- or inhibitor-mediated drug interactions. The major *CYP3A5* polymorphisms include the *CYP3A5*3, *6* and **7* alleles which are functionally inactive due to single nucleotide

Corresponding Author: Roy L. Hawke, Pharm.D., Ph.D., Division of Pharmacotherapy and Experimental Therapeutics, University of North Carolina School of Pharmacy, CB #7360, Kerr Hall Rm 3310, Chapel Hill, NC 27599-7360, Fax: 919-962-0644, Email: rhawke@email.unc.edu .

polymorphisms that result in either splice defects or the introduction of an early stop codon that result in reduced production of the full length active protein (Lamba et al., 2002; Wojnowski, 2004; Xie et al., 2004). *CYP3A5*1* is the only functional *CYP3A5* allele known to contribute to total CYP3A activity and the frequency of the *CYP3A5*1* allele has been shown to differ among ethnic groups (Kuehl et al., 2001). The *CYP3A5*1* allele has been associated with higher midazolam systemic clearance and tacrolimus dose requirements (Kuehl et al., 2001; Lin et al., 2002; Wong et al., 2004), and greater metabolism of quinidine and saquinavir (Mouly et al., 2005; Mirghani et al., 2006).

Less is known about the influence of the *CYP3A5*1* allele on susceptibility for drug interactions caused by different CYP3A inducers and inhibitors. Recently, the *CYP3A5*1* allele was shown to influence susceptibility to the inhibitory effects of fluconazole but only in a substrate-dependent manner (Isoherranen et al., 2007). We have previously noted a correlation between basal hepatic CYP3A activity and the inductive effects of dexamethasone in healthy volunteers using the erythromycin breath test (McCune et al., 2000). While the effect of *CYP3A5* polymorphism on the induction of CYP3A activity by glucocorticoids has not been explored, the presence of the *CYP3A5*1* allele does not appear to influence induction of hepatic CYP3A activity by the potent CYP3A4 inducer, rifampin when assessed by the systemic clearance of midazolam or by the ERBT (Floyd et al., 2003; Yu et al., 2004). We hypothesized that the influence of *CYP3A5* polymorphism on induction-type drug interactions could vary with different inducers. Therefore, the effect of an anti-emetic dose of dexamethasone on CYP3A activity, as determined by the erythromycin breath test, was compared to that of the prototypical inducer rifampin in a cohort of young, healthy African American volunteers prospectively genotyped for the presence of the *CYP3A5*1* allele.

MATERIALS AND METHODS

Study participants

Healthy, unrelated volunteers self-identified as African American (n = 84) were prospectively genotyped to identify potential study participants. The volunteers, ranging in age from 18–45 years, were genotyped for *CYP3A4*1B* and *CYP3A5*3*, **6*, and **7* alleles from a mouthwash sample using polymerase chain reaction-restriction fragment length polymorphism (Lin et al., 2002). Subjects were prospectively stratified according to *CYP3A5* genotype without regard to smoking status or to the presence of the *CYP3A4*1B* allele. To determine the effect of *CYP3A5* genotype on rifampin induction, 14 subjects were grouped according to the presence (*CYP3A5*1/*1* and **1/*3*, **1/*6*, or **1/*7*) or absence (*CYP3A5*3/*3* or *CYP3A5*3*, **6*, or **7/*6*, **7*) of the *CYP3A5*1* allele. Likewise, 12 subjects were similarly stratified to determine the effect of *CYP3A5* genotype on CYP3A induction by dexamethasone. Prior to enrollment, all subjects received a physical examination consisting of vital signs (pulse, blood pressure, respiration and body temperature), auscultation of heart and lungs and routine clinical laboratory tests. Individuals with a diagnosis or history of cancer, significant organ dysfunction or disease, HIV or taking medications known to induce or inhibit CYP3A were excluded. Individuals with risk factors for glucocorticoid-associated osteonecrosis, such as diagnosis or history of systemic lupus erythematous, recent radiation exposure, recent history of major trauma, history of steroid use in the previous 12 months, histological disease, gout/hyperuricemia or hyperlipidemia were excluded from participation in the dexamethasone treatment group. A negative tuberculin skin test was required for all subjects. In addition, a negative pregnancy test within seven days of ERBT administration was required for female subjects. No alcohol, herbal medications, or foods or beverages containing grapefruit juice were permitted for the duration of the study.

Study protocol

The study protocol was approved by the University of North Carolina Biomedical Institutional Review Board, and all subjects provided written informed consent before enrollment. This was a parallel design study that allowed crossover into the other treatment arm. After the screening visit, basal hepatic CYP3A activity was determined by the ERBT as previously described (Watkins et al., 1989), and the percent of the erythromycin dose exhaled per hour was calculated from the measured amount of [^{14}C]-CO_2 (Isoherranen et al., 2007). Subjects then received one of two CYP3A inducers for 5 days: rifampin 600mg orally once daily or dexamethasone 8mg orally twice daily and then on day 6 the ERBT was repeated. The extent of induction in the ERBT was calculated by expressing the difference between ERBT values, obtained before and after each inducer, as a percent of each subject's baseline ERBT.

Dexamethasone and rifampin were self-administered on an outpatient basis. Compliance was assessed through study calendars in which subjects documented the time of drug self-administration. Subjects qualifying and consenting to both inducer treatments underwent a minimum 14-day washout period between receipt of rifampin and dexamethasone. During the dexamethasone phase of the study, subjects were asked to monitor, daily, their blood pressure with a home monitoring cuff, as well as glucose levels with a urine dipstick kit. Subjects were contacted daily by phone during the induction phase to assess compliance, monitoring parameters and adverse events.

Statistical Analysis

All statistical analyses were performed using SAS-JMP (SAS Institute Inc, Cary, NC). The choice of sample size was guided by considerations of the expected statistical precision, expected power of the test procedure for the primary outcome which was selected based on findings from our previous study (McCune et al., 2000), study feasibility, cost, and the aims of the study. A sample size of 6 per group provided sufficient power to detect an effect size of 50%, however, a sample size of 8 per group was selected because of the uncertainty in the expected variance in an African American population identified by *CYP3A5* genotype status. The primary outcome, the effect of dexamethasone on the ERBT in a cohort who were non-carriers of the *CYP3A5*1* allele, was analyzed by use of a paired Student's *t*-test. We also determined the effect of dexamethasone on the ERBT in a cohort who carried the *CYP3A5*1* allele. The difference in the inductive effects of rifampin and dexamethasone between *CYP3A5*1* allele carriers and non-carriers were secondary endpoints for this study. In all analyses, $P < 0.05$ was considered statistically significant and data are presented as mean $\pm$ standard deviation. In the planning stage, estimated power curves were plotted as functions of plausible magnitudes of treatment effects and variance based on previous inductive effects observed with rifampin and dexamethasone (Gharaibeh et al., 1998; McCune et al., 2000).

RESULTS

CYP3A5 Genotyping

For the 84 subjects who were originally consented and genotyped for this study, the frequency of the *CYP3A5*1* allele was 66%. Genotype distribution showed 24 individuals carrying the *CYP3A5*1/*1* genotype (29%), 20 individuals carrying the *CYP3A5*1/*3* genotype (24%), 7 individuals carrying the *CYP3A5*1/*6* genotype (8.3%), and 4 carrying the *CYP3A5*1/*7* genotype (4.8%). One individual each was genotyped as *CYP3A5*6/*7* and *CYP3A5*6/*6*. Eight individuals carried the *CYP3A5*3/*6* genotype (9.5%), and 6 carried the *CYP3A5*3/*7* genotype (7.1%). The homozygous variant genotype, *CYP3A5*3/*3*, was carried by 13 individuals (15.5%). The frequency distributions of all *CYP3A5* alleles were in Hardy-Weinberg equilibrium ($p \geq 0.35$). These allelic frequencies were in agreement with previous reports involving African American subjects (Kuehl et al., 2001).

Linkage disequilibrium (LD) between *CYP3A4*1B* and *CYP3A5*1* alleles was not observed (D' = 0.025, Haploview ver3.11) when an additional 51 subjects genotyped for major *CYP3A4* and *CYP3A5* polymorphisms were pooled for a total of 135 African Americans for this analysis. This result was consistent with our observation from the HapMap data (http://www.hapmap.org) that *CYP3A4*1B* and *CYP3A5*1* genotypes were not in LD in African Americans when *CYP3A5* genotypes were visually sorted by *CYP3A4*1B* (data not shown).

Effect of *CYP3A5* Genotype on Extent of Induction

Of the 27 volunteers who consented to participate, 21 completed the study. Of the six dropouts, two in the rifampin arm did not return for treatment. In the dexamethasone arm, two did not return for treatment, and two withdrew after initiating dexamethasone treatment. Of these latter two subjects, one experienced irretractable hiccups beginning on day 3 of dexamethasone treatment, which lasted greater than 24 hrs but resolved 24 hours after discontinuing the dexamethasone; the other subject completed the 5-day course of dexamethasone but IV access could not be obtained to draw labs or administer the second ERBT. Fourteen subjects completed the rifampin arm of the study (7 *CYP3A5*1* carriers, 7 non-carriers), and 12 subjects completed the dexamethasone arm (6 carriers, 6 non-carriers). Three *CYP3A5*1* carriers and two non-carriers participated in both arms of the study.

To evaluate the influence of *CYP3A5* genotype on basal CYP3A activity, the basal ERBT values from both rifampin and dexamethasone arms of the study were pooled. For the five subjects who completed both arms of the study, the mean of both basal ERBT values (one from the rifampin arm and one from the dexamethasone arm) was included in a weighted least-squares analysis depicted in Figure 1. In addition, neither the level of significance nor conclusion was changed if either basal value for these five subjects was used in separate analyses. The mean basal ERBT value for all subjects was found to be significantly higher for individuals who carried at least one *CYP3A5*1* allele compared to individuals who lacked a *CYP3A5*1* allele (2.71% ± 0.53% versus 2.12% ± 0.37%, P = 0.006).

Rifampin significantly increased CYP3A activity in carriers of the *CYP3A5*1* allele from a baseline mean ERBT of 2.60 ± 0.66% to 4.68% ± 1.03% (P = 0.0008), and in non-carriers of the *CYP3A5*1* allele from a baseline mean ERBT of 2.11 ± 0.43% to 3.55% ± 0.9% (P = 0.0017) (Figure 2A). Similarly, and anti-emetic regimen of dexamethasone increased CYP3A activity in non-carriers of the *CYP3A5*1* allele from a baseline mean ERBT of 2.14 ± 0.31% to 3.03% ± 0.94% (P = 0.031) (Figure 2B). In contrast to the effect of rifampin, an increase in CYP3A activity following dexamethasone administration was not detected in African Americans who carried the *CYP3A5*1* allele (mean baseline ERBT of 2.83 ± 0.35% to 3.30% ± 0.85%, P = 0.160) (Figure 2B). Because baseline values differed between the two *CYP3A5* genotypes, the change from baseline to induced level of the ERBT was also compared between *CYP3A5*1* carriers and non-carriers for both inducers. The change in the ERBT following rifampin treatment was similar for both carriers (2.09 ± 1.02%) and non-carriers (1.44 ± 0.81%) of the *CYP3A5*1* allele. While an approximately 2-fold difference in the change in the ERBT was observed between *CYP3A5*1* carriers (0.47 ± 1.05%) and non-carriers (0.89 ± 0.91%) following administration of dexamethasone, this difference did not reach statistical significance due to greater variance observed with this inducer compared to rifampin.

Several studies have suggested that women have higher hepatic CYP3A activity (as measured by the ERBT) than men (Watkins et al., 1989; Watkins et al., 1992; Kinirons et al., 1999). In the dexamethasone arm of this study, all *CYP3A5*1* carriers were women, whereas 4 out of 6 of the *CYP3A5*1* non-carriers were women. In the rifampin arm, there were 6 women who were *CYP3A5*1* carriers and 5 who were non-carriers. To verify that sex effects on basal CYP3A activity did not account for differences observed with either inducer, we compared

basal ERBT values between women who were either carriers or non-carriers of the *CYP3A5*1* allele. Women who carried the *CYP3A5*1* allele had a significantly higher mean basal ERBT value compared to women non-carriers (2.84% versus 2.01%; P = 0.003). From this post-hoc analysis, we conclude that effects of the two inducers on CYP3A activity were not confounded by sex.

DISCUSSION

The current study was conducted in African Americans because of the higher frequency of the *CYP3A5*1* allele in this population, and to control for the effects of genetic admixture when subjects were stratified according to *CYP3A5*1* allele carrier status (Kuehl et al., 2001; Lamba et al., 2002; Zeigler-Johnson et al., 2004; Roy et al., 2005). The presence of CYP3A5 protein has been used to explain disease associations linked to the *CYP3A4*1B* allele since *CYP3A4*1B* and *CYP3A5*1* alleles appeared to be strongly linked in some populations. The *CYP3A5*1* allele did not appear to be in LD with the *CYP3A4*1B* allele in our study although strong LD has been observed in non-African populations (Thompson et al., 2006). Recently, the *CYP3A7*2* allele was shown to be in high LD with the *CYP3A5*1* allele in African Americans (Rodriguez-Antona et al., 2005; Thompson et al., 2006).

Our results suggest that African Americans carrying at least one *CYP3A5*1* allele had higher basal ERBT values compared to those lacking the *CYP3A5*1* allele, and differences in basal activity may be associated with difference in susceptibility for induction-type drug interactions with glucocorticoids. It has been estimated that CYP3A5 can account for 6% to 85% of total hepatic CYP3A content and may contribute to increases in basal CYP3A activity in individuals who carry a functional *CYP3A5*1* allele (Wrighton et al., 1990; Kuehl et al., 2001; Lin et al., 2002). Individuals carrying at least one *CYP3A5*1* allele exhibit a higher oral clearance, lower steady-state blood concentrations, and require higher tacrolimus doses to achieve therapeutic blood concentrations than patients lacking the *CYP3A5*1* allele (Bader et al., 2000; Hesselink et al., 2003; Thervet et al., 2003; Haufroid et al., 2004; Hesselink et al., 2004). Recent studies evaluating saquinavir, indinavir, and quinidine have found a positive correlation between the presence of a *CYP3A5*1* allele and higher oral clearance (Frohlich et al., 2004; Mouly et al., 2005; Anderson et al., 2006; Mirghani et al., 2006).

Similar to previous observations (Floyd et al., 2003; Yu et al., 2004), the *CYP3A5*1* allele was not associated with differences in the ability of rifampin to induce ERBT values in our African American cohort. In contrast, induction of ERBT values by dexamethasone was only detected in non-carriers of the *CYP3A5*1* allele. Differences in potencies between these two inducers could explain this observation. Compared to the potent inductive effects of rifampin on CYP3A4 protein, the inductive effects of a less potent PXR activator, such as dexamethasone, could be obscured if a large proportion of the total CYP3A activity was due to functional CYP3A5 since CYP3A5 expression is constitutive and not altered by PXR activation (Bertilsson et al., 1998; Lehmann et al., 1998; Burk et al., 2004). The proximal promoter of CYP3A5 contains a consensus ER-6 response element which may be important for its constitutive expression, although it lacks the distal PXR-response element shown to enhance transcription of CYP3A4 by xenobiotics (Goodwin et al., 2002; Burk and Wojnowski, 2004). Therefore, compared to CYP3A4, CYP3A5 appears to be less sensitive to induction by PXR activators and this has been confirmed in studies with human hepatocytes (Burk et al., 2004).

Several recent reports suggest the *CYP3A5*1* allele may impart important clinical consequences due to the higher clearance of some CYP3A drugs (Mouly et al., 2005; Isoherranen et al., 2007; Jin et al., 2007; Josephson et al., 2007). More recently, low hepatic CYP3A activity was found to be associated with the risk for corticosteroid-induced osteonecrosis (Kaneshiro et al., 2006). Our finding that *CYP3A5* polymorphism may influence

basal levels of hepatic CYP3A activity and the inductive effects of corticosteroids suggests that absence of *CYP3A5*1* alleles may be associated with risk for corticosteroid-induced osteonecrosis.

In summary, *CYP3A5* polymorphism appears to influence susceptibility to induction-type drug interactions for certain inducers, and *CYP3A5*1* non-carriers may be more susceptible to the inductive effects of dexamethasone due to lower CYP3A4-dependent basal activity. These results may be particularly relevant for patients undergoing chemotherapy and receiving dexamethasone for delayed nausea. Our data also suggests that *CYP3A5* genotype may have played a role in our previous finding of an inverse correlation between baseline hepatic CYP3A activity and the extent of CYP3A induction following a 5-day course of dexamethasone.

Non-Standard Abbreviations

CYP3A, cytochrome P450 3A subfamily; ERBT, erythromycin breath test; LD, linkage disequilibrium.

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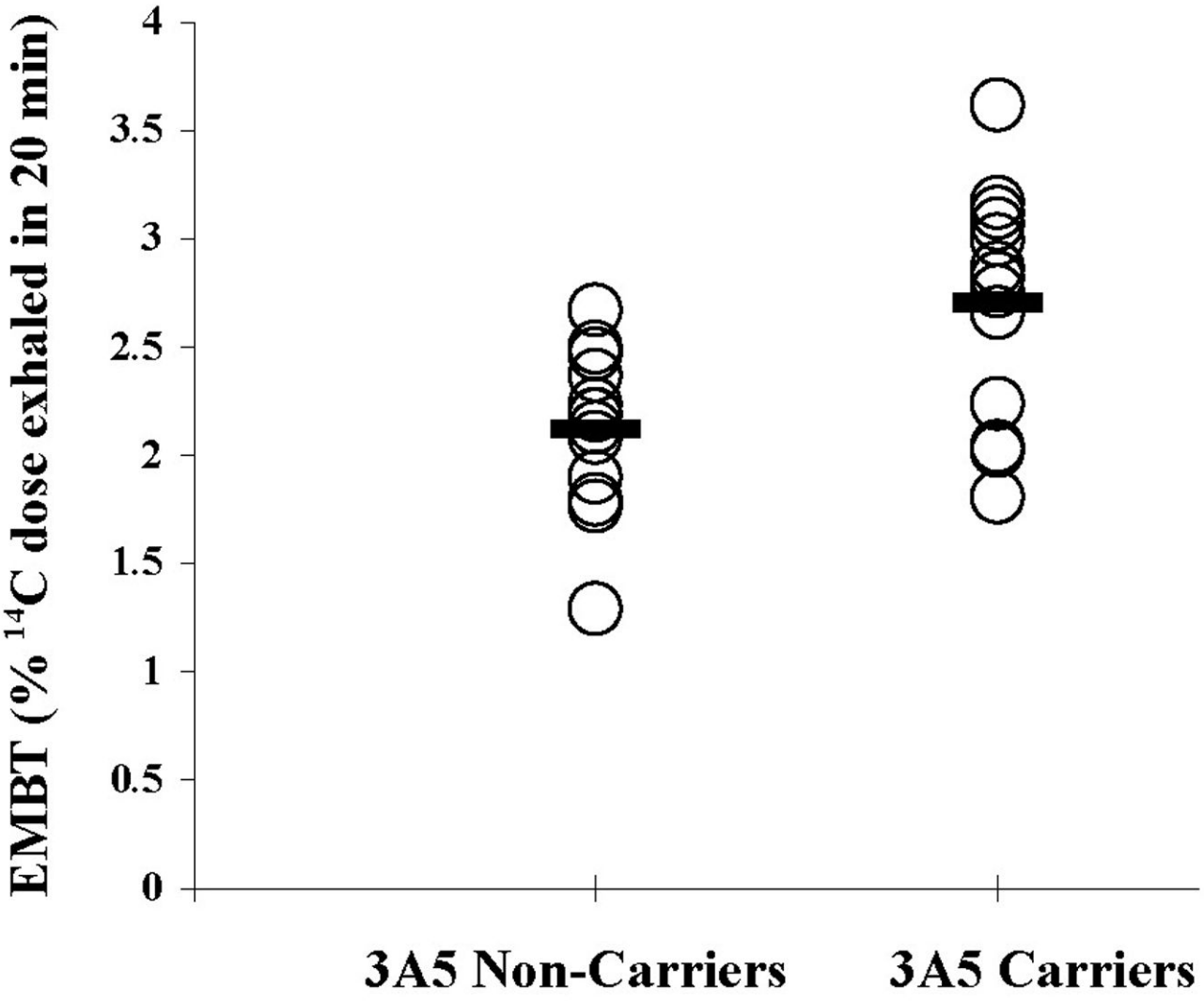

Figure 1. Effect of *CYP3A5* genotype on basal hepatic CYP3A activity as determined by the erythromycin breath test (ERBT)

The mean ERBT was significantly higher for *CYP3A5*1* carriers compared to non-carriers (2.71% ± 0.53% versus 2.12% ± 0.37%, P = 0.006) using a weighted least squares analysis to correct for 5 subjects who participated in both study arms. Open circles denote individual values. Closed bars denote the group mean.

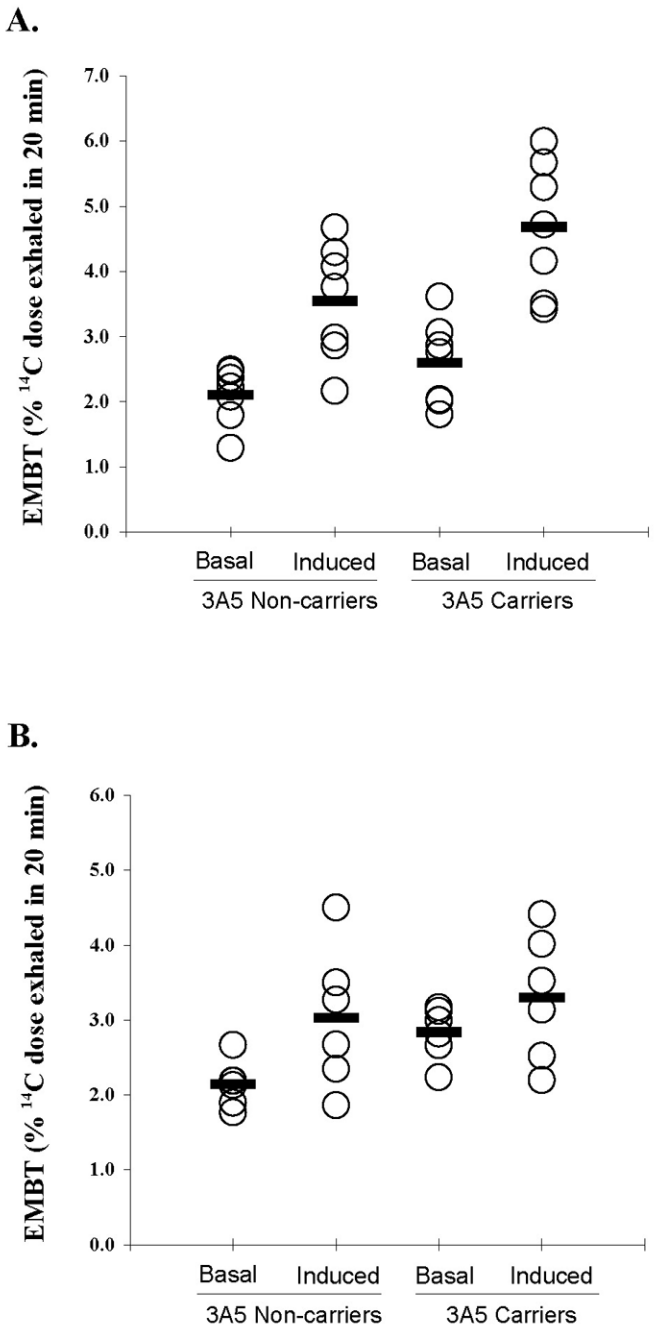

Figure 2. Effect of rifampin or dexamethasone on CYP3A activity in African Americans who were stratified according to *CYP3A5*1* allele carrier status

(A) Rifampin significantly induced CYP3A activity in non-carriers (P = 0.0017) and carriers (P = 0.0008) of the *CYP3A5*1* allele. (B) A significant increase in CYP3A activity was observed in *CYP3A5*1* non-carriers after dexamethasone administration (P = 0.031). In contrast, an effect of dexamethasone on CYP3A activity was not detected in *CYP3A5*1* carriers (P = 0.160). Open circles denote individual values. Closed bars denote the group mean.