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Pharmacokinetics of Phase I Nevirapine Metabolites following a Single Dose and at Steady State

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Nevirapine is one of the most extensively prescribed antiretrovirals worldwide. The present analyses used data and specimens from two prior studies to characterize and compare plasma nevirapine phase I metabolite profiles following a single 200-mg oral dose of nevirapine in 10 HIV-negative African Americans and a steady-state 200-mg twice-daily dose in 10 HIV-infected Cambodians. Nevirapine was assayed by high-performance liquid chromatography (HPLC). The 2-, 3-, 8- and 12-hydroxy and 4-carboxy metabolites of nevirapine were assayed by liquid chromatography-tandem mass spectrometry (LC/MS/MS). Pharmacokinetic parameters were calculated by noncompartmental analysis. The metabolic index for each metabolite was defined as the ratio of the metabolite area under the concentration-time curve (AUC) to the nevirapine AUC. Every metabolite concentration was much less than the corresponding nevirapine concentration. The predominant metabolite after single dose and at steady state was 12-hydroxynevirapine. From single dose to steady state, the metabolic index increased for 3-hydroxynevirapine ($P < 0.01$) but decreased for 2-hydroxynevirapine ($P < 0.001$). The 3-hydroxynevirapine metabolic index was correlated with nevirapine apparent clearance ($P < 0.001$). These findings are consistent with induction of CYP2B6 (3-hydroxy metabolite) and a possible inhibition of CYP3A (2-hydroxy metabolite), although these are preliminary data. There were no such changes in metabolic indexes for 12-hydroxynevirapine or 4-carboxynevirapine. Two subjects with the CYP2B6 *6*6 genetic polymorphism had metabolic indexes in the same range as other subjects. These results suggest that nevirapine metabolite profiles change over time under the influence of enzyme induction, enzyme inhibition, and host genetics. Further work is warranted to elucidate nevirapine biotransformation pathways and implications for drug efficacy and toxicity.

In resource-limited settings, the nonnucleoside HIV-1 reverse transcriptase inhibitor (NNRTI) nevirapine (NVP) is among WHO-recommended components of first-line antiretroviral therapy. At the time of this study, nevirapine in combination with two nucleoside reverse transcriptase inhibitors, such as stavudine or zidovudine, and together with lamivudine was the preferred regimen for treatment-naïve patients, in part because of the availability of a WHO-prequalified, low-cost, generic, fixed-dose combination (1, 2). In addition, single-dose nevirapine administered to pregnant, HIV-infected women at delivery has been widely prescribed to prevent mother-to-child transmission (3–6). Despite its major therapeutic benefits, treatment with nevirapine may cause severe hepatotoxicity and/or skin rash in some patients. Molecular mechanisms of nevirapine toxicity are incompletely understood, but a causal role of metabolites has been suggested (7, 8).

Despite its widespread use, there remain gaps in understanding of nevirapine metabolism and disposition. Its pharmacokinetic characteristics include a long plasma half-life after single-dose administration which decreases with repeated doses due to autoinduction of its biotransformation (6, 9–11). Nevirapine is 60% bound to plasma proteins, and elimination occurs mainly through oxidative metabolism. Five metabolites, including hydroxyl metabolites at positions 2, 3, 8, and 12 (Fig. 1) and 4-carboxynevirapine derived from the 12-hydroxy metabolite, have been identified. *In vitro* microsome data suggest that CYP3A is involved in 2-hydroxynevirapine formation and CYP2B6 is involved in 3-hydroxynevirapine formation (12). Several CYPs are involved in the other pathways (12, 13). These metabolites are eliminated in the urine as conjugates, mainly glucuronides (14). Relatively little is known regarding nevirapine biotransformation and metabolite disposition following a single dose and at steady state, in part due to the lack of a direct and sensitive assay (13, 15).

A sensitive liquid chromatography-tandem mass spectrometry (LC/MS/MS) assay was recently developed to quantitate the phase I metabolites of nevirapine (16). The present analyses applied this assay to specimens from two prior studies to characterize plasma nevirapine phase I metabolite profiles in two different situations, one involving a single 200-mg oral dose of nevirapine given to 10 HIV-negative African Americans and the other at steady state with a 200-mg oral dose twice daily in 10 HIV-infected Cambodians. We also compare metabolite profiles between these situations.

MATERIALS AND METHODS

Patients and study design. Data and specimens for these pharmacokinetic analyses were from individuals who had participated in two previously published studies (17, 18). This analysis was approved by the Na-

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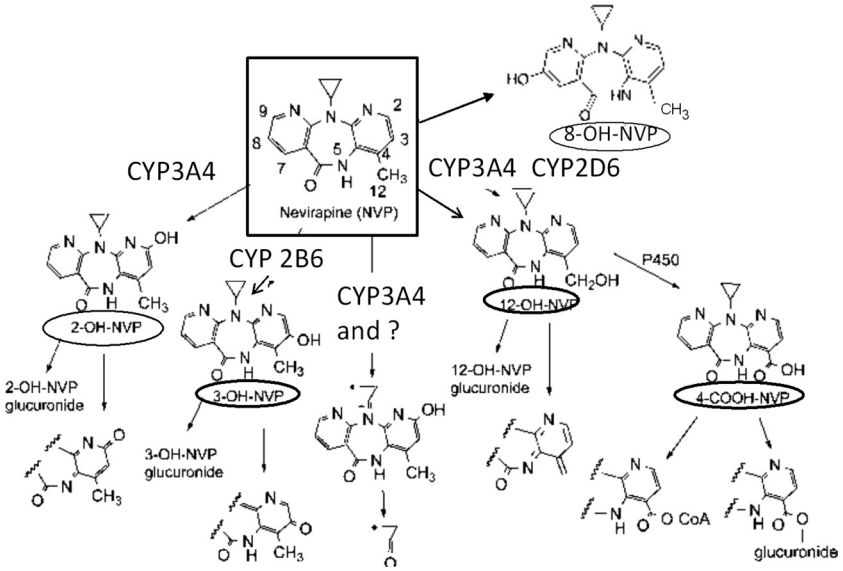

FIG 1 Structures of nevirapine (parent drug) and its 5 metabolites quantitated in this study (8).

tional Ethics Committee of Cambodia and by the Vanderbilt University Institutional Review Board. Plasma samples were from 10 healthy, HIV-negative African Americans (group A) who had received a single 200-mg oral dose of nevirapine (17) and from 10 HIV-infected Cambodians (group B) from the ESTHER (Ensemble pour une Solidarité Thérapeutique en Réseau) at the Calmette Hospital (Phnom Penh, Cambodia) (18). In both groups, plasma was kept frozen until analysis, and genotype data for *CYP2B6* *1*6 were available from the previous studies (17, 18).

Group B patients were on chronic, steady-state antiretroviral therapy with 200 mg nevirapine twice daily plus two nucleoside analogs (lamivudine with either stavudine or zidovudine) for about 3 years and agreed to participate in this extensive pharmacokinetic study as part of the ANRS12154 study. In that study, plasma HIV-1 RNA was measured in addition to standard laboratory tests.

Plasma samples from group A subjects were obtained at 0.5, 1, 2, 4, 6, 8, 12, and 24 h and on days 2, 3, 5, 7, 9, and 13 after a single dose of nevirapine. Plasma samples from group B subjects were collected at predose and at 1, 2, 4, and 8 h after the morning nevirapine dose.

Assay of nevirapine and metabolites in plasma. Plasma nevirapine assays for group A were performed in the United States (17), and those for group B were performed in Cambodia (18), both by liquid chromatography according to previously validated assays. The lower limit of quantification was 50 ng/ml. Standard curves were linear up to 5,000 ng/ml (17) or 10,000 ng/ml (18).

Nevirapine metabolites were assayed using a validated LC/MS/MS assay recently published by the Biomedical Mass Spectrometry Laboratory at the Ohio State University (16). The lower limit of quantification was 1 ng/ml for each hydroxy metabolite and 5 ng/ml for 4-carboxynevirapine. All concentrations were converted in molar equivalents based on molecular weights as follows: nevirapine, 266; hydroxy nevirapine, 282; and 4-carboxynevirapine, 292.

Pharmacokinetic analysis. Pharmacokinetic parameters for nevirapine and its phase I metabolites were assessed by noncompartmental methods (WinNonlin v6.1; Pharsight Corporation, Mountain View, CA). The linear-log trapezoidal method was used to calculate areas under concentration-time curves (AUCs) for group A to the last measurable concentration at time t ($AUC_{0\text{-}t}$) and for group B over a 12-hour dosing interval (AUC_{12}). For group B, we assumed identical predose and 12-hour postdose concentrations. For group A, the AUCs from t to infinity (AUC_{inf}) were calculated by extrapolation whenever determination of the terminal rate constant (λ_z) was possible. Apparent clearances of nevirapine (CL/F) were calculated by the following standard equations after single (SD) or repeated (SS) doses, respectively: $CL_{SD}/F = dose/AUC_{inf}$ or $CL_{SS}/F = dose/AUC_{12}$. The metabolic index was defined as the ratio of the metabolite AUC to the nevirapine AUC. For consistency in group A, the $AUC_{0\text{-}t}$ to the same last time t of concentration detection was used for metabolites and nevirapine to calculate metabolic indexes due to the inability to accurately determine the terminal rate constants (λ_z) for metabolites that were detected at very low concentrations. The maximum plasma concentration (C_{max}), the observed predose concentration (C_0), and the time to C_{max} (T_{max}) were obtained from visual inspection of concentration-time curves.

Statistical analyses. This observational pharmacokinetic study assessed plasma concentrations of nevirapine metabolites following single or repeated doses of nevirapine. When this pilot study was designed, there were no data to guide sample size estimates. We chose to study 10 individuals in each group to detect major differences in nevirapine metabolite disposition.

Pharmacokinetic parameters for nevirapine and its metabolites were described by medians and ranges. Parameters were compared between group A and group B using the nonparametric Wilcoxon rank-sum test. When appropriate, associations between pharmacokinetic parameters were examined using a Spearman correlation test. All analyses were performed using Statgraphics 5 plus (Manugistics, Inc., MD).

RESULTS

Study subject characteristics. Subject characteristics are summarized in Table 1. Group A comprised healthy, HIV-negative African Americans who received a single dose of nevirapine. Group B comprised HIV-infected Asians in Cambodia who were studied at steady state on nevirapine-containing regimens for at least 1 year. All patients had plasma HIV-1 RNA at <400 copies/ml at the time of study, and CD4 T cell counts ranged from 155 to 513 cells/μl (median, 277 cells/μl). Eight patients were receiving concomitant zidovudine and lamivudine, and two received concomitant stavudine and lamivudine. None of the patients were receiving medications that induce or inhibit drug-metabolizing enzymes (e.g., rifampin or fluconazole). In addition to race/ethnicity, the two populations differed by body mass index (BMI) and proportion of female participants. Frequencies of *CYP2B6* *1/*6 genotypes were

TABLE 1 Characteristics of study subjects

Characteristic	Values for HIV-negative adults in the United States ($n = 10$)	Values for HIV-infected adults in Cambodia ($n = 10$)
Race/ethnicity	African American	Cambodian
No. of females	8	5
Age (yrs) (range)	25 (21–43)	32 (28–44)
Weight (kg) (range)	68 (59–100)	52 (42–66)
BMI (range)	23 (18–33)	21 (19–22)
CYP2B6 *1/*6 (*n*)		
*1/*1	5	6
*1/*6	4	3
*6/*6	1	1

similar between groups, with one subject in each group being homozygous for *6/*6. All but one patient in group B had normal liver function tests (one with alanine aminotransferase [ALAT] of 99 IU/ml), and all had plasma creatinine of <1.1 mg/dl and calculated creatinine clearances of >60 ml/min.

Concentrations of nevirapine and its phase I metabolites. The within-day and day-to-day precisions of nevirapine quality control samples included in each analytical run were below 12%. Day-to-day precision of quality control of nevirapine metabolites was below 14%, and accuracy for between-run validation was within 93% and 116%. In groups A and B, plasma concentrations of each metabolite were well below concentrations of nevirapine at every time point (Fig. 2). Of the metabolites assayed, 12-hydroxynevirapine was the most abundant in both groups. Concentrations of 12-hydroxynevirapine were, on average, 5 times greater in group B than in group A, a result which parallels nevirapine concentrations. Concentrations of 3-hydroxynevirapine and 4-carboxynevirapine increased 5- to 20-fold in group B compared to those in group A. Interestingly, the 2-hydroxynevirapine concentration decreased from group A to group B. Plasma levels of 8-hydroxynevirapine were undetectable following a single dose of nevirapine. In contrast, measurable concentrations of 8-hydroxynevirapine were detected in all samples in group B, with a median C_{max} of 0.075 μM. Temporal declines in metabolite concentrations tended to parallel declines in nevirapine concentrations, indicating that the rate of metabolite formation is the rate-limiting step in their disposition and is driven by the slow elimination rate for nevirapine.

Pharmacokinetics of nevirapine metabolites. Pharmacokinetic parameters of nevirapine and its phase I metabolites are summarized in Table 2. As expected, the half-life of nevirapine was long in group A, with considerable interindividual variability (median, 99 h; range, 53 to 217 h). Although median half-lives of some metabolites tended to be shorter than that of nevirapine, these differences were not statistically significant. In group B, we were not able to calculate half-lives for nevirapine or its metabolites, as the dosing interval was too short.

The nevirapine AUC_{12} in group B was significantly less than the AUC_{inf} in group A, and the CL/*F* was significantly greater in group B than in group A (0.83 ml/min/kg and 0.29 ml/min/kg, respectively; $P < 0.001$), indicating nonlinear pharmacokinetics and autoinduction. The 3-hydroxynevirapine AUC_{12} in group B was greater than the 3-hydroxynevirapine AUC_{inf} in group A, although this difference was not significant. In contrast, the 2-hydroxynevirapine AUC_{12} was 95% lower in group B than the 2-hydroxynevirapine AUC_{inf} in group A ($P < 0.001$). The median AUC_{12} of 8-hydroxynevirapine was very low (0.76 μM · h) at steady state in patients of group B but could not be calculated in patients of group A. In contrast, 12-hydroxynevirapine and 4-carboxynevirapine AUC_{12} values were significantly lower in group B, representing approximately 30 and 40% of group A AUC_{inf} values, respectively. There was a correlation between AUCs of 4-carboxynevirapine and 12-hydroxynevirapine ($r = 0.82$, $P = 0.0003$). Metabolite indexes were compared between group A and group B (Fig. 3). The 2-hydroxynevirapine metabolite index was lower in group B than in group A ($P = 0.0002$), while the 3-hydroxynevirapine metabolite index was higher in group B than in group A ($P = 0.007$). In contrast, for 12-hydroxynevirapine and 4-carboxynevirapine metabolic indexes, there were no significant differences between group A and group B. In analyses involving all 20 study subjects, there were correlations between the apparent clearance of nevirapine and the metabolite indexes for 2-hydroxynevirapine ($r = -0.73$, $P = 0.0014$), 3-hydroxynevirapine

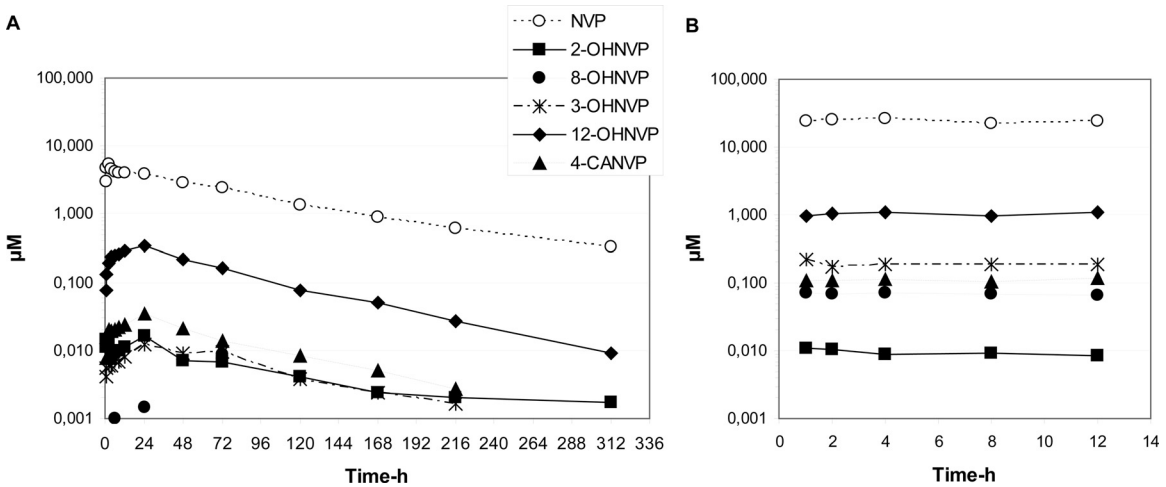

FIG 2 Median plasma concentrations of nevirapine and its 5 metabolites after single-dose administration of 200 mg of nevirapine (A) and at steady state during a 12-h dosing interval after administration of 200 mg of nevirapine twice daily (B).

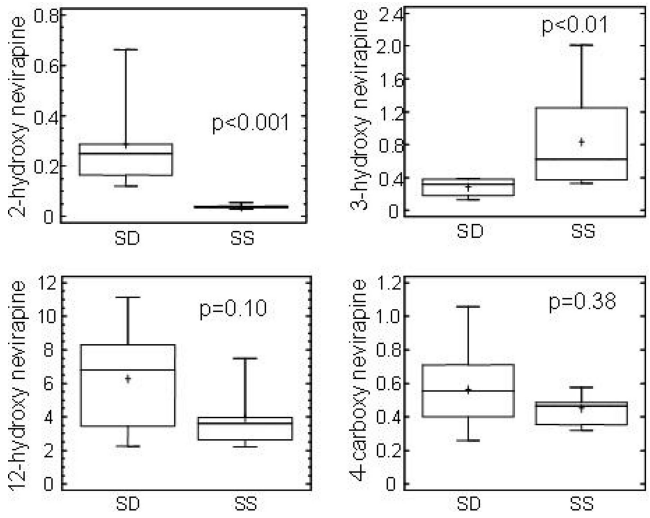

FIG 3 Box plots of metabolic indexes of nevirapine metabolites after single-dose administration of 200 mg of nevirapine (SD) and at steady state during a 12-h dosing interval after administration of 200 mg of nevirapine twice daily (SS).

($r = 0.63$, $P = 0.006$), and 12-hydroxynevirapine ($r = -0.47$, $P = 0.03$).

The 2 subjects carrying the *CYP2B6 *6*6* genotype had nevirapine and metabolite concentrations in the same range as the other subjects either after single-dose administration or at steady state.

DISCUSSION

This is the first study to describe the pharmacokinetics of nevirapine and its phase I metabolites after a single 200-mg dose of nevirapine and at steady state with the recommended 200-mg twice-daily dosing. The most important findings from this study are, first, the much lower concentrations of nevirapine metabolites compared to nevirapine and, second, the differential disposition of hydroxylated metabolites, possibly in keeping with the different CYPs involved in the nevirapine metabolic pathways (12). Interestingly, the effect of nevirapine induction on CYP2B6 activity leads to an increased concentration of 3-hydroxynevirapine and a lower concentration of the 2-hydroxynevirapine metabolite formed through the CYP3A pathway. The pharmacokinetic characteristics of parent nevirapine in the present study agree with those of previous studies conducted in patients or volunteers after a single dose or at steady state, a finding which clearly demonstrates the autoinducing properties of nevirapine (10, 19–27). Indeed, the two populations studied herein differ by their ethnicity, demographics, and HIV infection status; the *CYP2B6 *1*6* genetic polymorphism frequency is very close, but the significant difference remains when clearances are weight normalized (0.83 ml/min/kg versus 0.29 ml/min/kg). Low apparent nevirapine clearance suggests that biotransformation occurs mainly in the liver and that the intestinal first-pass effect is negligible. Consequently, as previously mentioned, the higher nevirapine clearance observed at steady state was due to a change in nevirapine metabolism rather than to altered bioavailability.

This study provides new information regarding unconjugated nevirapine metabolite disposition in plasma. After single dose or at steady state, concentrations are considerably less than those of

TABLE 2 Pharmacokinetic parameters of nevirapine and its metabolites after a single dose (group A) and at steady state (group B)

Drug	Pharmacokinetic parameters for[a]:									
	Group A after single dose						Group B at steady state			
	C_{max} (μM)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{12} (μM · h)	AUC_t (μM · h)	AUC_{inf} (μM · h)	C_{trough} (μM)	C_{max} (μM)	T_{max} (h)	AUC_{12} (μM · h)
Nevirapine	5.7 (3.8–12.1)	2 (0.5–8)	99 (53–217)	59.2 (38.0–66.9)	513.0 (380.0–592.0)	560 (430–684)	21.8 (13.5–36.5)	26.7 (19.1–50.2)	2 (0–4)	291.8* (161.9–459.8)
2-Hydroxynevirapine	0.02 (0.01–0.08)	1 (0.5–24)	99 (48–882)	0.10 (0.05–0.32)	0.97 (0.59–3.59)	1.55 (0.85–4.36)	0.01 (0.00–0.01)	0.01 (0.01–0.02)	2 (1–8)	0.11* (0.06–0.17)
8-Hydroxynevirapine	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	0.04 (0.03–0.08)	0.07 (0.05–0.14)	2 (1–14)	0.76 (0.46–1.29)
3-Hydroxynevirapine	0.01 (0.01–0.03)	24 (6–72)	59 (35–217)	0.09 (0.04–0.12)	1.14 (0.47–2.12)	1.37 (0.73–2.40)	0.11 (0.05–0.23)	0.18 (0.08–0.49)	1 (0–8)	1.76 (0.77–4.17)
12-hydroxy nevirapine	0.32 (0.14–0.72)	12 (2–24)	61 (43–1,221)	3.12 (1.10–5.16)	27.11 (12.47–54.92)	34.92 (14.17–78.17)	0.51 (0.18–2.67)	1.00 (0.50–3.81)	3 (1–12)	9.53** (4.18–34.42)
4-Carboxynevirapine	0.03 (0.02–0.12)	12 (2–24)	48 (25–81)	0.23 (0.12–0.46)	2.37 (0.82–6.88)	2.77 (0.90–7.24)	0.08 (0.03–0.21)	0.13 (0.09–0.27)	3 (1–14)	1.12** (0.75–2.65)

[a] Values are medians (ranges). *, $P < 0.001$ for the AUC_{12} at steady state compared to the AUC_{inf} after a single dose; **, $P < 0.01$ for the AUC_{12} at steady state compared to the AUC_{inf} after a single dose.

nevirapine. On one hand, the volume of distribution of polar metabolites should be close to or smaller than that of nevirapine, and on the other hand, a very high rate of glucuronide conjugate elimination is limited by their rate of formation from nevirapine or from 12-hydroxynevirapine for 4-carboxynevirapine. Consequently, different concentrations may be related to different rates of formation. This is in keeping with the previous findings of Riska et al. (14), who demonstrated that after autoinduction and administration of a single oral dose (solution) of 50 mg containing 100 mCi of [^{14}C]NVP, glucuronide conjugation and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. 2-Hydroxynevirapine glucuronide (18.6%), 3-hydroxynevirapine glucuronide (25.7%), and 12-hydroxynevirapine glucuronide (23.7%) were the major metabolites recovered in urine. They also showed that disposition of radioactivity was rate limited by biotransformation of nevirapine to its hydroxylated metabolites rather than by excretion of the metabolites into feces and urine, consistent with our results. Our plasma samples were not hydrolyzed; therefore, the plasma ratio of hydroxynevirapine to its glucuronide is not available in our study. A comparison of steady-state trough plasma concentrations in our patients with concentrations measured in HIV-infected patients with mild liver fibrosis (13) showed that nonconjugated 2-hydroxynevirapine and 3-hydroxynevirapine concentrations are well below those of the glucuronides, which remained lower than those of nevirapine, roughly 2 ng/ml versus 177 ng/ml and 12 ng/ml versus 759 ng/ml, respectively. In contrast, 8-hydroxynevirapine and 12-hydroxynevirapine concentrations are closed whether plasma was hydrolyzed or not (29 versus 31 ng/ml and 504 versus 142 ng/ml, respectively), indicating that glucuronide concentrations of these metabolites in plasma are low. Concentrations of 4-carboxynevirapine were low and in the same range, which is explained by the elimination of this metabolite unchanged in urine (14).

A comparison of concentrations of nevirapine metabolites or metabolic indexes after single-dose administration and at steady state provides insight into nevirapine disposition. Dispositions of the four hydroxylated metabolites differ, a result which may be related to different CYPs involved in their formation. *In vitro* data demonstrated that CYP3A and CYP2B6 were responsible for the formation of 2- and 3-hydroxynevirapine, respectively, while CYP3A and CYP2D6 participated to the formation of 8- and 12-hydroxynevirapine, respectively (12). Hepatic *CYP2B* genes represent the most-inducible CYP isoforms by phenobarbital-type compounds in most mammalian species (28, 29). Consequently, induction of CYP2B6 may explain the relative increase in 3-hydroxymetabolite concentrations compared to nevirapine and a significant increase in the metabolic index at steady state compared to the single dose. Surprisingly, the 2 subjects from groups A and B carrying CYP2B6 *6*6 did not have decreased concentrations of 3-hydroxynevirapine, suggesting that this variant may be inducible by nevirapine. CYP3A was identified as the unique CYP involved in the formation of 2-hydroxynevirapine, which surprisingly is decreased at steady state compared to the single dose. A recent investigation conducted in human liver microsomes revealed the formation of a quinine methide reactive intermediate which is subsequently attacked by glutathione to yield a sulfhydryl conjugate of nevirapine (30). This reactive intermediate was catalyzed primarily by CYP3A and possibly by CYP2D6, CYP2C19, and CYP2A6 and was shown to inactivate CYP3A with a K_i of 31 μM (about 8,000 ng/ml), not far from the average concentration of nevirapine at steady state. These *in vitro* data correspond to the clinical observation of potent attenuation of CYP3A induction and possibly to the decreased formation of 2-hydroxynevirapine. Such a dual mechanism of inhibition/inactivation and induction has been demonstrated for other drugs, such as ritonavir or nelfinavir (31, 32), although the net effect of those antiretroviral drugs is potent CYP3A inhibition, in contrast to nevirapine, for which induction of CYP2B6 is likely the primary pathway. Such a hypothesis is not supported by many drug-drug interaction studies (33). However, a 20% increase in rifabutin and desacetyl-rifabutin (CYP3A substrates) concentrations has been reported when coadministered with nevirapine (Viramune product information; Boehringer Ingelheim). Another explanation may be induction of 3-hydroxynevirapine-glucuronide formation. Whether such induction may be specific to one glucuronide pathway remains to be further explored. The exact contribution of different CYPs to the formation of 8-hydroxynevirapine and 12-hydroxynevirapine is unknown. Based on *in vitro* data, 8- and 12-hydroxynevirapine formation is predicted to involve CYP3A and CYP2D6. 8-Hydroxynevirapine was detected in plasma only at steady state. We would expect induction of this metabolic pathway by nevirapine, which is not supported by *in vitro* data, or, alternatively, a low rate of formation by noninducible CYP2D6 and accumulation at steady state (34, 35). A decreased AUC_{12} compared to the AUC_{inf} but no difference in metabolic indexes suggests a major contribution of noninducible CYP2D6 in the formation of 12-hydroxynevirapine.

Nevirapine use has been associated with severe skin rash and/or liver toxicity in some patients (36). It has been suggested from *in vitro* experiments and animal models that the 12-hydroxynevirapine pathway may be involved in nevirapine toxicity. An ultimate reactive metabolite for both liver toxicity and skin rash may be the quinone methide formed by CYP3A as previously mentioned (7, 8, 30). Conversely, recent toxicogenomics of nevirapine suggest fundamentally different mechanisms of adverse events: cutaneous, most likely major histocompatibility complex (MHC) class I-mediated and influenced by the *CYP2B6* nevirapine slow-metabolizer genotype, and hepatic, most likely MHC class II-mediated and unaffected by the *CYP2B6* genotype (37). Our study, involving a limited number of subjects, was not designed to compare metabolite exposure and occurrence of side events. Reactive metabolites may form in the liver or skin, so plasma 12-hydroxynevirapine concentrations may not be directly related to toxicity.

This study had several limitations. The studied populations have different characteristics, as the subjects represented different races/ethnicities, HIV statuses, and body mass indexes. The timing of blood sample collection differed, with intensive sampling following a single dose or sparse sampling at steady state. However, results of nevirapine pharmacokinetic parameters are consistent with those of previous studies, allowing comparison of metabolite pharmacokinetics. We did not characterize the glucuronidated metabolites either in plasma or urine, so we could not fully characterize the disposition of phase 1 and phase 2 metabolism of nevirapine.

In conclusion, this study demonstrates different dispositions of unconjugated plasma nevirapine metabolites after single-dose administration of nevirapine and at steady state. All concentrations are well below those of nevirapine, with 12-hydroxynevirap-

ine being the highest. Concentrations of 2-hydroxynevirapine, whose formation is CYP3A mediated, decreased from single dose to steady state, while those of 3-hydroxynevirapine, CYP2B6 mediated, increased from single dose to steady state. Clinical consequences of such findings are presently unknown and warrant further investigation.

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