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Nevirapine Significantly Reduces the Levels of Racemic Methadone and (R)-Methadone in Human Immunodeficiency Virus-Infected Patients

Hartmut Stocker,1,2* Guido Kruse,3 Peter Kreckel,4 Christian Herzmann,4 Keikawus Arasteh,1,2 Jörg Claus,4 Heiko Jessen,4 Christiane Cordes,4 Bettina Hintsche,4 Frank Schlote,4 Lothar Schneider,4 and Michael Kurowski1,2

Vivantes Auguste-Viktoria-Klinikum1 and EPIMED GmbH, c/o Vivantes Auguste-Viktoria Klinikum,4 HIV-Lab, c/o Vivantes Auguste-Viktoria Klinikum,4 and Kompetenznetz HIV/AIDS,2 Berlin, Germany

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Methadone is metabolized by various isoforms of the cytochrome P450 family, which can be induced by many drugs, including nevirapine. The objective of the present study was to determine the effects of coadministration of nevirapine and methadone on the dose-adjusted areas under the concentration-time curves (AUCs) of racemic and (R)-methadone. Twenty-five human immunodeficiency virus-infected subjects taking stable daily doses of racemic methadone or (R)-methadone were included in this prospective, single-crossover trial. At the baseline, nevirapine was either started as part of a new regimen containing two nucleoside reverse transcriptase inhibitors (NRTIs) or added to an ongoing NRTI regimen. Patients could increase their methadone doses if withdrawal symptoms developed. Twelve-hour pharmacokinetic profiles were obtained before and 28 days after the start of nevirapine treatment. The total concentrations of methadone and its inactive metabolite, EDDP, in serum were determined by liquid chromatography-tandem mass spectrometry. Among the 20 evaluable patients, coadministration of nevirapine significantly decreased the mean dose-adjusted AUC of methadone by 41%. AUC reductions were similar for patients taking racemic methadone (37%; n = 11) and (R)-methadone (44%; n = 9). AUC changes ranged from mild increases in three patients to decreases of up to 70%. Fourteen of 20 patients required additional methadone due to withdrawal symptoms. However, the median dose increase was only 15%, which was less than that which would have been expected from the pharmacokinetic data. The AUC of EDDP increased significantly, by 35%. Methadone dose adjustments are justified when methadone is coadministered with nevirapine. Due to extensive variability, the adjustments must be tailored to the individual patient’s needs.

MATERIALS AND METHODS

Subjects. Twenty-five HIV type 1-infected patients who were stably taking once-daily doses of methadone and who required antiviral therapy were enrolled in the study. The study design was approved by the ethics committee of the Berliner Ärztekammer. All participants gave their written informed consent. In order to be eligible, patients had to be taking either a treatment regimen consisting of nucleoside analogues (nucleoside reverse transcriptase inhibitors [NRTIs]) only or no antiretroviral therapy at all.

A complete medical history was taken at the screening visit, which was scheduled 3 weeks before the start of NVP treatment. A physical examination that included evaluation of vital signs and a routine safety laboratory examination with blood count, coagulation tests, blood chemistry, and urinalysis were performed. Three days before the start of the treatment period, an alcohol breath test and a screening of urine for the presence of illicit drugs were performed.

Subjects were ineligible for this study if they had a history of pancreatitis or neuropathy within 6 months before screening, treatment for a malignancy within 18 months before screening, or ongoing antiretroviral therapy. No subject was currently taking a drug with a potential interaction with methadone. Potential subjects were excluded if they had taken a prohibited substance within 14 days before screening. Subjects with a history of treatment-refractory hepatitis C, HIV-associated neurocognitive disorders, or hormone deficiency were also excluded. Substances used as an anxiolytic were allowed if the patient had a history of at least 6 months of opioid dependence. The study was approved by the ethics committee of the Berliner Ärztekammer.

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An electronic randomization system was used to ensure that the study was double-blinded. A total of 125 treatment combinations were generated, and the treatment assignments were randomly assigned to the subjects. The study was designed to quantify the effect of coadministration of NVP on the pharmacokinetics of methadone and its main metabolite, EDDP.

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30 days before screening, or any major clinically significant abnormality. Patients were also excluded if they were consuming alcohol or using illicit drugs before or during the study period. Patients requiring treatment with medications and herbal substances known to interfere with hepatic drug metabolism were also ineligible. Additionally, patients were told to abstain from drinking alcohol and grapefruit juice before and during the study period.

**Study design.** The primary endpoint of this trial was the intraindividual comparison of the dose-corrected AUCs from 0 to 12 h (AUC0-12) of methadone without and with NVP. The 12-h interval covers the largest fraction of the total AUC that includes the maximum concentration. Therefore, AUC0-12 is a sensitive parameter for the detection of pharmacokinetic interactions in this particular once-daily dosing regimen.

This was a prospective, open-label, multiple-dose, single-crossover, two-period study conducted at the EPI-MED clinical trials unit of the Vivantes Auguste-Viktoria Klinikum and associated physicians in Berlin, Germany. The study consisted of a 21-day screening period, a 28-day treatment period, and a follow-up period. Treatment consisted of nevirapine at 200 mg once a day for 14 days and 200 mg twice a day (BID) for the following 14 days and thereafter. NVP was either started in combination with two NRTIs or added to an ongoing NRTI regimen. On day 0, eligible patients were admitted to the clinical trials unit. Patients were asked to attend in a fasted state. Standardized meals and beverages were provided during the following 12 h. Patients reported the time of their last methadone dose on the previous day. Serial blood samples were taken from each subject for the generation of the plasma methadone and EDDP concentrations. The sample collection took place on days 1, 7, 8, and 12 postdosing. The majority (80%) of the effluent was split off before it entered the autosampler. HPLC separation was achieved by mobile phase gradient elution of 1.0 ml/min. The majority (80%) of the effluent was split off before it entered the interface. An API 365 mass spectrometer (Applied Biosystems, Toronto, Ontario, Canada) equipped with an electrospray ionization ion source and run with Analyst (version 1.2) software was used for detection. Analysts were monitored in the positive multiple-reaction monitoring mode with the following transitions of precursor to product ions: m/z 310.15 to 265.30 (methadone), 278.00 to 234.30 (EDDP), and 319.15 to 268.20 (deuterium-labeled methadone).

Standards and quality control samples were prepared in blank serum. For each batch, two eight-point standard calibration curves for samples containing methadone and EDDP at concentrations ranging from 20 to 2,500 ng/ml and NVP at concentrations ranging from 41 to 5,300 ng/ml were prepared in duplicate. Quality control samples containing all analytes at concentrations of 250 and 1,000 ng/ml were prepared. Inter- and intraday coefficients of variation for methadone, EDDP, and NVP were <2, <7, and <5%, respectively, at concentrations of 1,000 ng/ml and <8, <8, and <8%, respectively, at concentrations of 250 ng/ml. Mean deviations from nominal concentrations were below 8% for all analytes and concentrations throughout the entire analysis.

**Statistics.** AUCs were calculated by the trapezoidal rule. Intraindividual AUC changes were analyzed with and without adjustment for methadone doses. Median interquartile ranges (IQRs), means, and 95% confidence intervals (CIs) were calculated for each parameter. Means and CIs for the pharmacokinetic profile and for intraindividual AUC changes were backcalculated from log-transformed data. This procedure was chosen because log-transformed AUC data were assumed to be normally distributed. The paired t test was used to test for nonzero differences for the values obtained before the initiation of NVP treatment and those obtained after 28 days of NVP treatment for the complete study population, patients taking racemic methadone, and patients taking (R)-methadone. The reported p values are two sided.

**RESULTS**

Twenty-five patients were included in the study, which was conducted between March 2001 and September 2002. Five subjects were excluded during and after the treatment phase because of protocol violations [one subject because of intravenous use of methadone, two subjects because they had started NVP treatment before day 0, and two subjects because they had changed from racemic methadone to (R)-methadone during the study period]. None of the subjects withdrew due to adverse events.

Table 1 summarizes the characteristics of the 20 remaining subjects. Eleven subjects were taking racemic methadone, and
nine were taking (R)-methadone. The median methadone doses for the subgroups taking racemic methadone and (R)-methadone were 140 mg (range, 35 to 220 mg) and 75 mg (range, 45 to 115 mg), respectively. The median dose of the active enantiomer in the total study population was 72.5 mg (range, 45 to 115 mg).

No clinically relevant alterations were detected in any of the individuals during the physical examination and routine safety laboratory tests. Urine pHs were comparable on the two pharmacokinetic sampling days (day 0, pH 5.6; day 28, pH 5.6).

### TABLE 2. Methadone doses, dose-adjusted AUCs, and AUC changes

<table>
<thead>
<tr>
<th>Treatment and patient no.</th>
<th>Dose (mg) without/with NVP</th>
<th>AUC [ng · h/ml]/mg</th>
<th>% AUC/dose change</th>
<th>% Actual dose change</th>
<th>% Theoretical dose change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without NVP</td>
<td>With NVP</td>
<td>Without NVP</td>
<td>With NVP</td>
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<td>17.2</td>
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<td>48.7</td>
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Median (IQR) 46 (43 to 58) 31 (22 to 41) -35 (-53 to -8) 14 (6 to 34) 56 (9 to 111)

(R)-Methadone

<table>
<thead>
<tr>
<th>Treatment and patient no.</th>
<th>Dose (mg) without/with NVP</th>
<th>AUC [ng · h/ml]/mg</th>
<th>% AUC/dose change</th>
<th>% Actual dose change</th>
<th>% Theoretical dose change</th>
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<td>With NVP</td>
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<td>72.4</td>
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</table>

Median (IQR) 50 (42 to 79) 28 (21 to 39) -45 (-56 to -41) 17 (0 to 20) 83 (69 to 126)

AUC/dose ratio during NVP therapy was 41% lower than that without NVP therapy [mean intrasubject AUC decrease, 21 (ng · h/ml)/mg; 95% CI, 16 to 26 (ng · h/ml)/mg; P < 0.001]. For the group of patients taking racemic methadone, the mean AUC decreased by 37% [mean intrasubject AUC decrease, 18 (ng · h/ml)/mg; 95% CI, 9 to 25 (ng · h/ml)/mg; P < 0.05]. In the group of patients taking (R)-methadone, the mean dose-adjusted AUC during NVP administration was 44% lower than that without NVP administration [mean intrasubject AUC decrease, 26 (ng · h/ml)/mg; 95% CI, 21 to 31 (ng · h/ml)/mg; P < 0.001]. Figure 2 summarizes the results and shows the mean

![](image.png)
intraindividual AUC decreases and 95% CIs. Table 2 provides the corresponding medians and IQRs for each of the parameters. AUC changes were highly variable, ranging from slight increases in two patients to reductions of 70% (Table 2).

The dose-adjusted mean AUC of EDDP increased from 3.7 (ng · h/ml)/mg to 5.0 (ng · h/ml)/mg \((P < 0.05)\). AUC changes were similar in both groups. After 28 days of antiretroviral treatment, the median trough NVP level was 3,640 ng/ml (IQR, 3,410 to 4,630 ng/ml). The NVP treatment was well tolerated by all study participants. Clinically relevant events associated with the medication, in particular, rash and clinical symptoms of hepatotoxicity, were not reported. Alanine aminotransferase and aspartate aminotransferase values did not change significantly throughout the whole study period, but there was a significant and continuous increase in gamma glutamyltransferase levels, from a median of 49 U/liter on day 0 to a median of 58 U/liter on day 28.

**DISCUSSION**

Methadone is subject to hepatic metabolism. Previous data from in vitro experiments with human liver microsomes suggested that methadone is demethylated by the 3A4 isoform of the cytochrome P450 family (21, 26). These data suggest that the coadministration of drugs which inhibit 3A4 would lead to a rise in methadone exposure and to opiate intoxication. However, clinical trials which investigated the pharmacokinetics of methadone when it was coadministered with the CYP3A4 inhibitors indinavir, nelfinavir (NFV), and ritonavir (RTV) failed to confirm this assumption. Coadministration of indinavir did not lead to any change in methadone levels (8). Coadministration of NFV led to a decrease in methadone concentrations (20), and the AIDS Clinical Trials Group ACTG 401 trial found that there was a reduction in methadone levels when it was coadministered with saquinavir (SQV)-RTV (400/400 BID), the latter being a very strong inhibitor of CYP3A4 (17).

When given alone, RTV (100 mg BID) had no influence on methadone levels at all (25). Inducers of CYP3A4 also failed to show the expected effects on methadone concentrations: in a study with patients receiving rifabutin, methadone levels remained unchanged (6). These surprising results, together with recent in vitro data, suggest that the principal cytochrome of methadone metabolism may not be CYP3A4 but CYP2B6, followed by CYP2C19 (16). In addition, in vitro and in vivo evidence suggests that methadone metabolism is stereoselective (13–16, 22, 24, 31, 35). CYP2B6 has been shown to preferentially metabolize the inactive \((S)\)-isomer, CYP2C19 has been shown to preferentially metabolize the active \((R)\)-isomer, and CYP3A4 has been shown to preferentially metabolize both isomers (16, 31, 35). Stereoselective metabolism may partly account for the fact that amprenavir reduces total methadone concentrations without provoking signs and symptoms of opioid withdrawal. A trial which investigated the effect of amprenavir on methadone levels in 16 healthy subjects showed that the AUC of the active isomer decreased by only 12%, whereas the AUC of the inactive \((S)\)-methadone was reduced by 40%. The opioid pharmacodynamic measures recorded in this trial were unchanged, and none of the participants complained of withdrawal symptoms (19). Patients who took NFV or SQV-RTV with methadone also had greater decreases in the levels of the inactive isomer. Again, these patients did not experience opioid withdrawal (17, 20). However, SQV-RTV elevated the fraction of unbound methadone by displacing it from protein binding. This effect, which may also occur with NFV-methadone coadministration, could be an alternative explanation for the absence of withdrawal symptoms (17). Two studies with patients taking methadone and lopinavir-RTV reported significant reductions in methadone AUCs (36% [10] and 26% [25]). Even though the data are conflicting, lopinavir-RTV administration does not seem to
cause withdrawal symptoms in the majority of patients taking methadone. Neither study measured the levels of the methadone enantiomers.

NVP is metabolized by CYP3A4, CYP2B6, and CYP2C19 but has no inhibitory effect on any of these enzymes when it is present at therapeutic concentrations (34). In vivo, NVP seems to induce the levels of expression of some of these cytochromes, but confirmatory data are scarce (23, 32; unpublished data from Boehringer Ingelheim).

The assay that we developed for this study was not stereoselective. However, 9 of our 20 patients were taking the methadone formulation, which contains only (R)-methadone. Reductions in methadone AUCs were similar in both patients receiving racemic methadone and those receiving (R)-methadone. Among the patients in both groups, all but three patients suffered from withdrawal symptoms. There was a slightly greater decrease in the AUC in the group of patients taking (R)-methadone than in the group of patients taking racemic methadone, but this difference was not significant. Under the assumption that CYP3A4 may play a less important role in methadone metabolism, our results would indicate that CYP2B6 and possibly CYP2C19 are induced by NVP. This is consistent with the finding that the CYP2B6 inducer efavirenz also reduces methadone concentrations (12).

The NVP trough levels measured in this study are similar to historical data (33), which indicates that patients were adherent to their medication regimens and that the interaction was unidirectional.

It has previously been observed (11) that patients need to increase their methadone doses during NVP therapy much less than would have been expected from pharmacological data. In our total study population, a theoretical median dose increase of 79% would have been required to compensate for the reduction in AUCs. This is in contrast to the median dose increase of 15%. Six subjects did not require any change in their methadone doses, despite significant reductions in methadone exposure. It has been suggested that a gradual detoxification from methadone occurs during NVP treatment (11). Our data strengthen this hypothesis because, after having increased their methadone exposure, some of the patients may have had methadone levels well above the threshold concentration at which point withdrawal symptoms occur. A reduction in the level of methadone exposure may have been tolerated by these individuals because the levels still remained above this threshold.

The policy concerning methadone dosing during this study permitted physicians to increase the dose according to the patients’ needs. Therefore, it is likely that these data reflect the real need for additional methadone during NVP administration. However, no general recommendation can be given as to how much and when the dose of methadone should be increased. Therapeutic drug monitoring of methadone does not seem to be helpful because there is no clear correlation between the pharmacokinetics of methadone and its opioid effects. Decisions must be based on clinical grounds, and dose increases need to be individualized and should not be undertaken unless the patient complains about withdrawal symptoms, since severe intoxications leading to death have occurred during methadone treatment (7, 9). When symptoms occur, additional methadone should be allowed with increments in small steps of 5 or 10 mg.

ACKNOWLEDGMENTS

This trial was sponsored by Boehringer Ingelheim. The development of the assay and sample analysis were supported by the German Bundesministerium fu¨r Bildung und Forschung, BMBF (Kompetenz-netz HIV/AIDS grant 01 KI 0211). We thank Steffi Lehmann, Renate Rogall, the EPIMED team, and the patients. Special thanks go to Thomas Fischer.

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