Investigation of the Interactions between Methadone and Elvitegravir-Cobicistat in Subjects Receiving Chronic Methadone Maintenance

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Interactions between HIV and opioid dependence therapies are known to occur. We sought to determine if such interactions occurred between methadone and elvitegravir boosted with cobicistat (EVG/COBI). We performed a within-subject open-label pharmacokinetic and pharmacodynamic study of 11 HIV-seronegative subjects stabilized on at least 2 weeks of methadone. Subjects underwent baseline and steady-state evaluation of the effect of elvitegravir 150 mg once a day (QD) boosted with 150 mg QD of cobicistat (EVG/COBI) on methadone pharmacokinetic parameters. Safety and pharmacodynamics were monitored throughout the study. Compared to baseline values, the R-methadone mean area under the concentration-time curve to the end of the dosing period \( (AUC_{\text{tau}}) \) (5,550 versus 6,210 h · ng/ml) and mean maximum concentration of drug in serum \( (C_{\text{max}}) \) (316 versus 337 ng/ml) did not significantly increase in the presence of EVG/COBI. Compared to baseline values, the S-methadone mean \( AUC_{\text{tau}} \) (7,040 versus 7,540 h · ng/ml) and mean \( C_{\text{max}} \) (446 versus 452 ng/ml) did not significantly increase in the presence of EVG/COBI. The \( AUC_{\text{tau}} \), \( C_{\text{max}} \), and \( C_{\text{tau}} \) of elvitegravir and cobicistat did not significantly differ from those of historical controls. Opioid withdrawal or overdose was not observed among subjects in this study. The addition of EVG/COBI to stabilized patients receiving methadone did not affect methadone pharmacokinetics and pharmacodynamics. These two agents can be safely coadministered.

Substantial advances in the treatment of opioid dependence have been made in recent years. These have had a favorable impact on clinical and public health outcomes of patients with both opioid dependence and HIV/AIDS (1, 2). Medication-assisted treatment with methadone or buprenorphine improves adherence to antiretroviral therapy and is effective for both primary and secondary HIV prevention (3, 4). The number of people eligible for and receiving treatments for both opioid dependence and HIV infection has increased. Co-administration of these therapies, however, has been associated with both pharmacokinetic (PK) and pharmacodynamic interactions, with important clinical consequences (5, 6). The concern about such interactions may deter some patients or providers from initiating potentially life-saving therapy (7). Such interactions may lead to nonadherence with antiretroviral regimens, development of viral resistance, and a lack of efficacy of HIV therapy (5, 6). Opioid-dependent patients may also experience adverse effects from HIV treatment that mimic opioid withdrawal and may relapse to opioids or other illicit substances (e.g., cocaine and alcohol) to alleviate symptoms. The occurrence of unrecognized drug interactions may therefore lead to a lack of success of treatment for HIV, opioid dependence, or both.

Methadone is a full mu-opioid agonist used for the treatment of opioid dependence (9). Methadone is administered as a racemic of \( R \) and \( S \) enantiomers, with the \( R \) enantiomer having the greater potency at the mu-opioid receptor (10). Methadone undergoes oxidative metabolism to inactive metabolites by several cytochromes, including cytochrome P450 2B6 (CYP2B6), CYP3A4, CYP2C19, CYP2D6, and CYP2C8 (11–17). Substantial interindividual variation exists (18, 19); therefore, changes in methadone plasma concentrations do not necessarily predict the pharmacodynamic response. Specifically, a similar change in plasma concentrations may produce withdrawal symptoms in one patient and none in another. Such unpredictability is multifactorial and may be the result of varying protein displacement, stereospecific binding, and the expression levels of relevant metabolic enzymes and transporters (15, 20). This variability makes predicting specific pharmacological interactions problematic.

Elvitegravir (EVG), an HIV-1 integrase inhibitor, is primarily metabolized by CYP3A and is a modest inducer of CYP2C9 (21, 22). Cobicistat (COBI), a structural analogue of ritonavir, is a potent irreversible mechanism-based inhibitor of CYP3A without activity against HIV and a moderate inhibitor of CYP2D6 (23). COBI also inhibits the following transporters: P-glycoprotein (P-gp), BCRP, OATP1B1, and OATBP1B3 (22). COBI was developed to facilitate once-daily coadministration and is currently coformulated with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) into the EVG/COBI/FTC/TDF single-tablet regimen indicated for the treatment of antiretroviral-naive, HIV-infected adults.

MATERIALS AND METHODS

Study design. This was a multiple-dose, open-label, sequential, nonrandomized study of methadone-maintained HIV-negative subjects. Subjects were eligible if they were (i) HIV-seronegative, (ii) \( \geq 18 \) and \( \leq 60 \) years of age, (iii) had a body mass index (BMI) of 19 to 34 kg/m\(^2\), (iv) were not being treated with concomitant medications that might alter drug disposition, (v) stabilized for a minimum of 2 weeks at a methadone dose between 80 and 120 mg once daily, and (vi) without clinically significant medical conditions, as determined by medical history, physical examination, electrocardiogram (ECG), complete blood count, hepatic transaminases, and creatinine and were not pregnant. Urine toxicity for amphetamines, benzodiazepines,
TABLE 1 Pharmacokinetic parameters before and after steady-state elvitegravir-cobicistat in patients maintained on buprenorphine

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Treatment mean (% CV) for</th>
<th>Geometric least-squares mean ratio (%)</th>
<th>90% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>R-Methadone(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC(_{\text{tau}}) (ng · h/ml)</td>
<td>6,211.6 (43.7)</td>
<td>5,547.6 (21.3)</td>
<td>106.98</td>
</tr>
<tr>
<td>C(_{\text{max}}) (ng/ml)</td>
<td>336.9 (46.4)</td>
<td>316.4 (21.4)</td>
<td>101.41</td>
</tr>
<tr>
<td>C(_{\text{SS}}) (ng/ml)</td>
<td>234.0 (55.7)</td>
<td>196.6 (25.0)</td>
<td>110.00</td>
</tr>
<tr>
<td>S-Methadone(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC(_{\text{tau}}) (ng · h/ml)</td>
<td>7,542.1 (56.1)</td>
<td>7,036.3 (39.8)</td>
<td>100.17</td>
</tr>
<tr>
<td>C(_{\text{max}}) (ng/ml)</td>
<td>452.4 (51.9)</td>
<td>445.8 (35.1)</td>
<td>95.92</td>
</tr>
<tr>
<td>C(_{\text{SS}}) (ng/ml)</td>
<td>260.0 (71.0)</td>
<td>229.8 (49.5)</td>
<td>102.19</td>
</tr>
</tbody>
</table>

\(^a\) Methadone plus EVG/COBI (test) versus methadone alone (reference). \(n = 11\).

\(^b\) CV, coefficient of variation.

TABLE 1: Pharmacokinetische parameters before and after steady-state elvitegravir-cobicistat in patients maintained on buprenorphine.

- **R-Methadone**
  - AUC\(_{\text{tau}}\) (ng · h/ml): Test 6,211.6 (43.7), Reference 5,547.6 (21.3), Geometric least-squares mean ratio 106.98, 96.06–119.16.
  - C\(_{\text{max}}\) (ng/ml): Test 336.9 (46.4), Reference 316.4 (21.4), Geometric least-squares mean ratio 101.41, 90.75–113.32.
  - C\(_{\text{SS}}\) (ng/ml): Test 234.0 (55.7), Reference 196.6 (25.0), Geometric least-squares mean ratio 110.00, 94.84–127.58.

- **S-Methadone**
  - AUC\(_{\text{tau}}\) (ng · h/ml): Test 7,542.1 (56.1), Reference 7,036.3 (39.8), Geometric least-squares mean ratio 100.17, 89.38–112.26.
  - C\(_{\text{max}}\) (ng/ml): Test 452.4 (51.9), Reference 445.8 (35.1), Geometric least-squares mean ratio 95.92, 86.62–106.23.
  - C\(_{\text{SS}}\) (ng/ml): Test 260.0 (71.0), Reference 229.8 (49.5), Geometric least-squares mean ratio 102.19, 89.24–117.01.

\(^a\) Methadone plus EVG/COBI (test) versus methadone alone (reference). \(n = 11\).

\(^b\) CV, coefficient of variation.

Cocaine, marijuana, opiates, and oxycodone was performed at baseline and repeated prior to the drug disposition studies being conducted. Subjects who screened positive for any of these substances in the urine toxicology were excluded from further evaluation. Except for EVG/COBI pharmacokinetics, subjects served as their own controls. At baseline, subjects on steady-state methadone were hospitalized and underwent pharmacokinetic investigation over a 24-h inpatient period. Blood specimens were drawn predose and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 h after dosing. During the inpatient hospitalization period, all subjects had standardized meals administered at the same time from medication dosing to minimize any effect of food relative to the pharmacokinetic parameters.

Study procedures included standardized measures of opioid withdrawal and opioid excess utilizing the objective opioid withdrawal scale (OOWS), subjective opioid withdrawal scale (SOWS), the clinical opioid withdrawal scale (COWS), and the opioid overdose assessment scale (OOAS) (24, 25). These scales were administered on a daily basis by trained nursing staff prior to the morning dose administration of methadone and EVG/COBI. Adverse symptoms were recorded in a standardized manner. This study was approved by the Institutional Review Board of Yale University.

**Bioanalytical procedures.** Concentrations of EVG, COBI, R-methadone, and S-methadone in plasma samples were determined using validated high-performance liquid chromatography-tandem mass spectrometry (LC/MS) bioanalytical methods at QPS, Inc. (Newark, DE). Sample analyses for EVG were performed as follows. Fifty microliters of human plasma was spiked with deuterated internal standard and processed by solid-phase extraction. The lower limit of quantitation for EVG was 20 ng/ml. COBI was analyzed in 50 μl of human plasma spiked with a deuterated internal standard followed by liquid-liquid extraction with methanol. The lower limit of quantitation for COBI was 5 ng/ml.

Sample analyses for R- and S-methadone were performed as follows. Three hundred microliters of human plasma was spiked with a deuterated internal standard followed by liquid–liquid extraction with methanol. The lower limit of quantitation for R- and S-methadone was 0.1 ng/ml.

**Pharmacokinetic and statistical analyses.** A sample size of 8 subjects could provide at least 94% power to conclude there was no PK alteration in R- or S-methadone in terms of the area under the concentration-time curve to the end of the dosing period (AUC\(_{\text{tau}}\)) and maximum concentration of drug in serum (C\(_{\text{SS}}\)) with a boundary of 70% to 143%; however, in order to have a reliable assessment of safety and pharmacodynamics, a total of 11 subjects were enrolled. Plasma concentration and PK parameters were summarized using descriptive statistics for each analyte by treatment (i.e., methadone plus EVG/COBI versus methadone alone).

Natural logarithm transformation of concentrations and AUC\(_{\text{tau}}\), C\(_{\text{max}}\), and C\(_{\text{SS}}\) to the end of the dosing period (C\(_{\text{SS}}\)) for each analyte (i.e., R-methadone, S-methadone, COBI, and EVG) were applied for pharmacokinetic analysis. A parametric (normal theory) analysis of variance (ANOVA) using a mixed-effects model was fitted to the natural logarithmic transformation of AUC\(_{\text{tau}}\), C\(_{\text{max}}\), and C\(_{\text{SS}}\) of R- and S-methadone. The 90% confidence intervals (90% CIs) were constructed for the ratio of geometric means of each of the pharmacokinetic parameters (AUC\(_{\text{tau}}\), C\(_{\text{max}}\), and C\(_{\text{SS}}\) of R- and S-methadone between methadone plus EVG/COBI (test treatment) and methadone alone (reference treatment). The pharmacokinetics of EVG and COBI were compared with historical data when coadministered in healthy volunteers (26).

**RESULTS**

**Study disposition.** Twelve individuals (8 males and 4 females; 11 Caucasian, 1 Black, 4 Hispanic, and 8 non–Hispanic) consented to the study, and 1 withdrew consent before taking any study drug and was therefore excluded from this analysis. Median (minimum to maximum) age, height, weight, and body mass index were 36 (22 to 45) years, 170.0 (161.3 to 174.8) cm, 80.7 (65.1 to 104.1) kg, and 28 (23.2 to 34.0) kg/m², respectively. None of the subjects developed adverse events requiring study discontinuation.

**Pharmacokinetic outcomes.** Pharmacokinetic data for R-methadone are summarized in Table 1 and graphically represented in Fig. 1. The mean AUC\(_{\text{tau}}\) of R-methadone did not significantly increase after the coadministration of EVG/COBI (5,550 versus 6,210 h · ng/ml, respectively). The geometric least-

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**FIG 1** The time versus plasma concentration plots of R-methadone before and after elvitegravir-cobicistat (EVG/COBI) administration. Means and standard deviations (SD) are shown.
The time versus plasma concentration plots of S-methadone before and after elvitegravir-cobicistat (EVG/COBI) administration. Means and standard deviations (SD) are shown.

FIG 2. The time versus plasma concentration plots of S-methadone before and after elvitegravir-cobicistat (EVG/COBI) administration. Means and standard deviations (SD) are shown.

squares (GLS) mean ratio was 107 with a 90% CI of 96 to 119. The $C_{\text{max}}$ (316 versus 337 ng/ml; GLS mean ratio, 101; 90% CI, 91 to 113) and $C_{\text{tau}}$ (197 versus 234 ng/ml; GLS mean ratio, 110; 90% CI, 95 to 128) also did not differ statistically before and after the administration of EVG/COBI.

Pharmacokinetic data for S-methadone are also summarized in Table 1 and graphically represented in Fig. 2. Compared to baseline values, the AUC$_{\text{tau}}$ of S-methadone did not significantly increase after the coadministration of EVG/COBI (7,040 versus 7,540 h · ng/ml, respectively). The geometric least-squares (GLS) mean ratio was 100 with a 90% CI of 89 to 112. The $C_{\text{max}}$ (446 versus 452 ng/ml; GLS mean ratio, 96; 90% CI, 87 to 106) and $C_{\text{tau}}$ (230 versus 260 ng/ml; GLS mean ratio, 102; 90% CI, 89 to 117) also did not differ statistically before and after the administration of EVG/COBI.

The AUC$_{\text{tau}}$, $C_{\text{max}}$, and $C_{\text{tau}}$ of EVG and COBI are in the range of historical data in healthy subjects and HIV-infected patients. In a previous phase 1 study evaluating EVG/COBI in healthy subjects, for example, the mean EVG AUC$_{\text{tau}}$, $C_{\text{max}}$, and $C_{\text{tau}}$ were 19,000 h · ng/ml, 2,150 ng/ml, and 318 ng/ml, respectively, while the mean COBI AUC$_{\text{tau}}$, $C_{\text{max}}$, and $C_{\text{tau}}$ were 10,400 h · ng/ml, 1,400 ng/ml, and 32.3 ng/ml, respectively (26). Additionally, across phase 2 and 3 studies in HIV-infected patients, the mean EVG AUC$_{\text{tau}}$, $C_{\text{max}}$, and $C_{\text{tau}}$ were 23,000 h · ng/ml, 1,700 ng/ml, and 450 ng/ml, respectively, while the mean COBI AUC$_{\text{tau}}$, $C_{\text{max}}$, and $C_{\text{tau}}$ were 8,300 h · ng/ml, 1,100 ng/ml, and 50 ng/ml, respectively (22).

Clinical pharmacodynamic outcomes. The OOWS, SOWS, COWS, and the OOAS were used to monitor the clinical effects of coadministration of methadone with EVG/COBI. These instruments were utilized before and throughout coadministration with EVG/COBI. No significant signs of withdrawal or excess occurred during the course of this study, and no dosage adjustments for methadone were required. Mean scores pre- and postadministration of EVG/COBI (day 1/day 10) for each validated instrument are listed as follows with their respective standard deviations: OOWS, 1.1 ± 1.38/0.2 ± 0.60 (maximum, 13); SOWS, 2.5 ± 3.45/0.4 ± 0.92 (maximum, 64); COWS, 1.5 ± 2.21/0.5 ± 0.93 (maximum, 48); and OOAS, 0.5 ± 0.52/0.1 ± 0.30 (maximum, 32).

DISCUSSION

In this study, coadministration of EVG/COBI with methadone did not significantly alter the pharmacokinetic parameters of EVG/COBI or methadone in HIV-seronegative subjects. As a structural analogue of ritonavir, COBI has greater specificity than ritonavir for CYP3A4. A previous study with ritonavir, a potent CYP3A4 inhibitor, also found no significant interaction between methadone and ritonavir (27). This is consistent with growing literature on the limited role of CYP3A4 in methadone metabolism. Kharasch and colleagues recently demonstrated that CYP2B6 is of greater importance in the metabolism of methadone than CYP3A4 (17). Methadone undergoes oxidative metabolism to inactive metabolites by several other cytochrome P450 variants, including CYP2C19, CYP2D6, and CYP2C8 (11–17). COBI is not an inhibitor of CYP2B6; however, it is a moderate inhibitor of CYP2D6 (22). Metabolism at CYP2B6, CYP2C19, and CYP2D6 is stereoselective; CYP2B6 and CYP2D6 favor S-methadone, while CYP2C19 favors R-methadone (14, 15, 28). The lack of differential plasma concentrations between R- and S-methadone before and after the addition of EVG/COBI in this study suggests either that CYP2D6 is not a significant site of methadone metabolism or that other compensatory enzymatic processes exist to counterbalance the effects at these sites. If compensatory mechanisms exist to explain these findings, one hypothetical scenario could involve CYP2B6. Because CYP2B6 preferentially metabolizes S-methadone and is not inhibited by COBI, CYP2B6 might compensate for inhibition at CYP2D6 thereby preventing differences in the ratio of R- to S-methadone plasma concentrations. In summary, the lack of significant changes in methadone plasma concentrations with COBI further supports the limited role of CYP3A4 in methadone metabolism and the lack of differences in the R/S-methadone ratio suggests a limited role for CYP2D6. Furthermore, these data suggest a lack of inductive effects of EVG/COBI on CYP2C19 and CYP2B6.

EVG/COBI are currently coformulated with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) into the EVG/COBI/FTC/TDF single-tablet regimen indicated for the treatment of HIV-1 infection in adults who are antiretroviral treatment naive. The fixed-dose combination was not studied because the components FTC and TDF are not expected to interact with methadone and did not significantly impact the plasma concentrations of methadone in 13 patients on methadone for a minimum of 2 weeks (30). Based upon the current data, it is believed that the coformulation of EVG/COBI/TDF/FTC can be safely coadministered without dosage modification to patients on methadone maintenance.

The results from this study are subject to several limitations. First, the sample size was powered for a 30% change in methadone plasma concentrations, as this was believed to be a level at which patients would experience pharmacodynamic symptoms. Smaller changes in plasma concentrations may not have been found due to the sample size; however, the current sample size is within the range of similar drug-drug interaction studies. Second, this study utilized a within-subject design with patients acting as their own controls (thereby resulting in less intrapatient variability); however, given this study design, it was not possible to directly compare the effects on EVG/COBI parameters before and after methadone administration. This comparison necessitated a less precise between-subject comparison with the use of historical controls.
Nevertheless, the results of these comparisons with the study subjects were not significantly different.

**Conclusion.** The addition of elvitegravir boosted with cobicistat to stabilized HIV-uninfected patients receiving methadone maintenance did not significantly alter the pharmacokinetic parameters of methadone. Elvitegravir-cobicistat levels in these subjects did not differ appreciably from those in historical controls. Methadone and elvitegravir-cobicistat can be safely coadministered without dosage modification.

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Gilead Sciences, Inc., owns elvitegravir and cobicistat. There are no additional relationships (financial or otherwise) with any other organizations that might have an interest in the submitted work in the previous 3 years; there are no other relationships or activities that could appear to have influenced the submitted work.

**REFERENCES**


