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

R. Douglas Bruce,a P. Winkle,b J. M. Custodio,a X. Wei,a M. S. Rhee,a B. P. Kearney,a S. Ramanathan,a Gerald H. Friedlanda

Yale University AIDS Program, New Haven, Connecticut, USAa; Anaheim Clinical Trials, Anaheim, California, USA; Gilead Sciences, Inc., Foster City, California, USA

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\textsubscript{tau}) (5,550 versus 6,210 h \cdot ng/ml) and mean maximum concentration of drug in serum (C\textsubscript{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\textsubscript{tau} (7,040 versus 7,540 h \cdot ng/ml) and mean C\textsubscript{max} (446 versus 452 ng/ml) did not significantly increase in the presence of EVG/COBI. The AUC\textsubscript{tau}, C\textsubscript{max}, and C\textsubscript{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. Coadministration 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 formulated 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) ≥18 and ≤60 years of age, (iii) had a body mass index (BMI) of 19 to 34 kg/m\textsuperscript{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 toxicology for amphetamines, benzodiazepines,

Received 12 June 2013 Returned for modification 8 August 2013 Accepted 20 September 2013 Published ahead of print 30 September 2013 Address correspondence to R. Douglas Bruce, rdouglasbruce@mac.com.

Copyright © 2013, American Society for Microbiology. All Rights Reserved.
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 fora)</th>
<th>Geometric least-squares mean ratio (%)</th>
<th>90% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-Methadone*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUCtau (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>Cmax (ng/ml)</td>
<td>336.9 (46.4)</td>
<td>316.4 (21.4)</td>
<td>101.41</td>
</tr>
<tr>
<td>Ctau (ng/ml)</td>
<td>234.0 (55.7)</td>
<td>196.6 (25.0)</td>
<td>110.00</td>
</tr>
<tr>
<td>S-Methadone*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUCtau (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>Cmax (ng/ml)</td>
<td>452.4 (51.9)</td>
<td>445.8 (35.1)</td>
<td>95.92</td>
</tr>
<tr>
<td>Ctau (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.

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 AUCtau 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-

in order to have a reliable assessment of safety and pharmacodynamics data, 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 AUCtau, Cmax, and Ctau to the end of the dosing period (Ctau) 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 logarithm transformation of AUCtau, Cmax, and Ctau 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 (AUCtau, Cmax, and Ctau) 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).

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.
MD  

Pharmacokinetic data for S-methadone are also summarized in Table 1 and graphically represented in Fig. 2. Compared to baseline values, the AUCmax 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 107 with a 90% CI of 96 to 119. The Cmax (316 versus 337 ng/ml; GLS mean ratio, 101; 90% CI, 91 to 113) and Ctau (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.

The AUCmax, Cmax, and Ctau 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 AUCmax, Cmax, and Ctau were 19,000 h · ng/ml, 2,150 ng/ml, and 318 ng/ml, respectively, while the mean COBI AUCmax, Cmax, and Ctau 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 AUCmax, Cmax, and Ctau were 23,000 h · ng/ml, 1,700 ng/ml, and 450 ng/ml, respectively, while the mean COBI AUCmax, Cmax, and Ctau 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 naïve. The fixed-dose combination was not studied because the components FTC and TDF are not expected to interact with methadone. FTC has not been formally studied with methadone because its metabolic pathway indicated a low probability of interaction. FTC has been used in HIV-infected patients on methadone without report of clinical interaction (29). TDF was studied 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.

**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.

**TABLE 1** Pharmacokinetic data for S-methadone, FTC, and TDF with EVG/COBI therapy. Means and standard deviations are shown.
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.

**ACKNOWLEDGMENTS**

All authors have completed the Unified Competing Interest form available on request from the corresponding author and declare Gilead Sciences, Inc., and the National Institutes of Health (R01 DA025932) provided funding for the submitted work.

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**