Effect of Prednisone on the Pharmacokinetics of the Integrase Inhibitor Dolutegravir

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Prednisone, a corticosteroid frequently used to treat common AIDS-related illnesses and comorbidities, has been shown to induce drug metabolism. This study was performed to determine whether prednisone coadministration affected the pharmacokinetics of dolutegravir (DTG). In this open-label, repeat-dose study, 12 healthy subjects were administered DTG at 50 mg daily alone for 5 days and then with concomitant prednisone for 10 days (prednisone at 60 mg daily for 5 days, followed by a 5-day taper). Serial blood sampling and safety assessments were performed during the trial. Pharmacokinetic parameters were determined using noncompartmental methods and geometric least-square mean ratios, and 90% confidence intervals were generated. Coadministration of DTG and 5-day high-dose prednisone with a 5-day taper had a modest effect on DTG exposure. The area under the DTG plasma concentration-time curve, maximum observed DTG concentration, and 24-hour postdose DTG concentration were increased by 11%, 6%, and 17%, respectively, on day 10 of the combination. Similar results were observed after 5 days of DTG and prednisone. Dolutegravir and prednisone coadministration was well tolerated. The changes in plasma exposures of DTG in healthy individuals as a result of prednisone dosing were not clinically significant. No dose adjustment is required for DTG coadministered with prednisone. (This study has been registered at ClinicalTrials.gov under registration no. NCT01425099.)

Targeting HIV integration of viral DNA into the human genome has yielded a new class of antiretroviral agents, the HIV integrase inhibitors, which have been used successfully in combination with other antivirals to suppress HIV replication (1–3). Dolutegravir (DTG; Viiv Healthcare, Research Triangle Park, NC) is a once-daily HIV integrase inhibitor with effective antiviral activity and a favorable safety profile. Dolutegravir is metabolized primarily by UDP-glucuronosyltransferase (UGT), with CYP3A4 playing a minor role (4). Dolutegravir has a favorable drug interaction profile, with few dose adjustments required, although potent enzyme inducers can reduce DTG exposure (5).

Prednisone is used to treat a number of AIDS-related illnesses, such as immune reconstitution inflammatory syndrome, Pneumocystis jirovecii pneumonia, AIDS-related lymphoma, and concomitant diseases such as asthma, chronic obstructive pulmonary disease, autoimmune/rheumatologic disease, inflammatory bowel disease, and cancers (6–10).

Some corticosteroids have been shown to decrease the exposure of UGT and CYP3A4 substrates (11, 12), depending on the choice of steroids, dose, and duration. Daily prednisone treatment of 40 mg/m² for 28 days increased etoposide clearance by 62% compared with placebo (13). Six-day treatment with low-dose prednisone (10 mg twice daily) modestly decreased metronidazole exposure, by 31% (14). Treatment with another corticosteroid, dexamethasone, at 1.5 mg for 4 days reduced oral triazolam AUC by 19% (15), whereas 2-day dexamethasone treatment at 24 mg per day decreased the praziquantel maximum observed plasma concentration (Cmax) by 43% 1.5 h after a praziquantel dose of 50 mg/kg of body weight (16). Although some of these studies did not have well-controlled crossover designs, these observations demonstrate that corticosteroids can modify UGT and CYP3A4 metabolism.

In vitro studies showed that DTG did not inhibit or induce UGT (4) and therefore is unlikely to affect corticosteroid pharmacokinetics (PK). However, a study to assess the possibility that prednisone alters DTG PK through UGT or CYP3A induction was warranted given the widespread use of corticosteroids in the HIV-infected population.

MATERIALS AND METHODS

Study design and participants. This study was a repeat-dose, open-label, parallel-group, 2-period study of 12 healthy adult males and nonpregnant, nonlactating females between September 2011 and October 2011 (ClinicalTrials.gov registration no. NCT01425099). Participants between 18 and 65 years of age, with a body weight of ≥50 kg for males and 45 kg for females and a body mass index within the range of 18.5 to 31.0 kg/m², were eligible. Healthy participants were considered eligible for inclusion based on a physical exam, medical history, electrocardiogram, and laboratory evaluation.

Participants were excluded because of a positive test for HIV antibody; enrollment in a recent clinical trial; evidence of hepatitis B or hepatitis C virus infection, or both, within 3 months of screening; history of any illness potentially exacerbated by corticosteroid administration; or a history of a preexisting condition that could interfere with the absorption, metabolism, and/or excretion of the study drugs. Consumption of nonprescription drugs (e.g., antacids, vitamins, and herbal and dietary supplements), red wine, Seville oranges, grapefruit, or grapefruit juice was prohibited from 14 days prior to the first dose of study medication through the duration of the trial, including follow-up.

The study was conducted at a single clinical site (Buffalo Clinical Research, Buffalo, NY). Written informed consent was obtained from all participants, and the protocol was approved by the institutional review board at each site.

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board of the study site. In period 1, each participant received 50 mg of DTG after a moderate-fat breakfast (30% fat content) for 5 days. In period 2, each participant received 50 mg of DTG and 60 mg of prednisone for 5 days, followed by tapered doses, reduced by 10 mg/day, for an additional 5 days. Blood samples for determining total DTG plasma concentrations were collected at the end of period 1 and on days 5 and 10 of period 2. Safety was assessed by clinical and laboratory evaluations throughout the study and at follow-up, 7 to 14 days after the last DTG and prednisone dose.

Bioanalytical methods. Plasma samples were extracted by protein precipitation with acetonitrile containing 1[^15]N[^4]H[^2]DTG as the internal standard. The plasma extracts were injected onto a 2.1-mm by 50-mm by 3.5-mum XBridge C18 column (Waters Associates, Milford, MA) and eluted with a mobile phase consisting of 40% acetonitrile in aqueous 0.1% formic acid. The eluate was detected using a Sciex API-4000 instrument (AB Sciex, Framingham, MA) equipped with a TurboIonSpray ionization source in the positive ion mode, with multiple-reaction monitoring (DTG m/z 420 > 277, internal standard m/z 428 > 277). Data acquisition and processing were performed with Analyst 1.4.2 software (AB Sciex), and linear regression analysis calculations were performed using Watson LIMS, version 6.4.0.04 (Thermo Scientific, Philadelphia, PA). The calibration range for DTG was 0.020 µg/ml to 20 µg/ml. Quality control samples, prepared separately at 0.06, 1.6, and 16.0 µg/ml, were stored with study samples and analyzed with each batch of samples against separately prepared calibration standards. The bias for the analysis of DTG was −1.8% to −0.3%, with precision values of 2.0% to 7.6% (within day) and ±1.9% (between days).

Pharmacokinetic analysis. A noncompartmental PK analysis of the concentration-time data was performed with WinNonlin (version 5.2; Pharsight Corp., Mountain View, CA). Pharmacokinetic parameters for DTG were calculated using the actual recorded times for each treatment. Pharmacokinetic parameters included area under the concentration–time curve from time zero to the end of the dosage (AUC(t)), C max, 24-hour postdose concentration (C(tmax)), apparent oral clearance (CL/F), apparent terminal half-life (t(1/2)), and time to maximum plasma concentration (T(max)).

Statistical analysis. Statistical analysis was performed on the log-transformed PK parameters AUC(t), C max, C(tmax), CL/F, and t(1/2). Analysis of variance (ANOVA) was performed using the SAS (Cary, NC) linear mixed-model procedure to assess the effect of prednisone on the PK of DTG. Subject was fitted as a random effect, and treatment was fitted as a fixed effect in the model. The ratio of geometric least-square means and associated 90% confidence intervals (CIs) were estimated for each PK parameter. Dolutegravir given alone was considered to be the reference treatment, and DTG coadministered with prednisone was considered to be the test treatment.

RESULTS

Demographics. A summary of demographic data is provided in Table 1. Seven female and five male healthy subjects were enrolled, and all subjects completed the study. Five of the subjects were Caucasian, and five were African American. The mean age was 28.5 years (range, 23 to 38 years), and the mean body mass index was 24.4 kg/m² (range, 18.9 to 29.6 kg/m²).

Safety. Study drugs were well tolerated in repeat doses of 50 mg daily for DTG and up to 60 mg daily for prednisone. No deaths, serious adverse events (SAEs), or withdrawals due to adverse events (AEs) were reported. The most commonly reported drug-related AE was headache, reported by 3 subjects (2 subjects with headache and 1 subject with migraine). The other drug-related AE was abnormal dreams, reported by 1 subject. All 4 drug-related AEs were reported in period 1 (DTG at 50 mg daily).

During treatment, all clinical laboratory abnormalities were grade 1 or 2. One grade 2 clinical laboratory value was reported: decreased hemoglobin in 1 subject during period 1 (day 5). The most common grade 1 clinical laboratory value was decreased albumin, which was present in 4 subjects. A grade 3 creatine phosphokinase elevation (3,267 U/liter; normal range, 0 to 180 U/liter) was reported in a follow-up visit and was attributed to physical exertion. Within 7 days, creatine phosphokinase levels improved, reaching the upper limits of normal (258 U/liter).

Pharmacokinetics. Mean concentration-time profiles of DTG alone and with prednisone are shown in Fig. 1. Pharmacokinetic parameters and statistical analyses for DTG are shown in Tables 2 and 3, respectively. Coadministration of high prednisone doses with DTG did not significantly alter AUC(t), C max on day 5 or day 10 of prednisone treatment, as the mean ratios were approximately 1.0 and the 90% CIs were between 0.8 and 1.25. Dolutegravir C(t) was increased by 21% after 5 days of high-dosage prednisone and by 17% after the 5-day prednisone dosage taper. Elimination half-life and CL/F were not significantly affected by prednisone administration.

DISCUSSION

Concomitant use of corticosteroids and antiretrovirals is common in HIV-infected patients. Prednisone is the standard choice for corticosteroid adjunctive therapy for Pneumocystis pneumonia among patients with AIDS and is commonly used for multiple other indications (17). It was chosen for this study based on its frequent clinical use in the HIV population and on prior reports of reduced plasma concentrations of other drugs metabolized through CYP3A4 and UGT1A1 in drug interaction studies (13, 14). This study demonstrated that a high dose of prednisone (60 mg daily) for 5 days, followed by a 5-day taper, was well tolerated and modestly increased several DTG PK parameters, in contrast to the expected direction of the interaction. Thus, no clinically significant enzyme induction was observed during administration of prednisone for 10 days. The small increase in DTG exposure was not clinically relevant, suggesting that DTG and prednisone can be coadministered without DTG dosage adjustment.

Although the prednisone dosage to treat Pneumocystis pneumonia (40 mg twice daily for 5 days, 40 mg daily for 5 days, and 20 mg daily for 11 days) (17) is greater than the dosage used in this
study (60 mg daily for 5 days, followed by a 5-day taper), safety considerations determined the study dosage. The prednisone dosage selected was considered high enough to result in enzyme induction but low enough to provide an acceptable risk-benefit profile for a healthy subject population. In addition, prednisone treatment at a range of doses up to 60 mg daily is commonly prescribed for multiple indications relevant to patients with HIV infection (9).

Extrapolation of these short-term results to prolonged coadministration should be considered. On the basis of simulations of trial designs for CYP3A4 inducers (18, 19), an assumed CYP3A4 turnover half-life of 36 h (20), the short half-life of prednisone, and the high prednisone dosage used in this study, there is no evidence to suggest that continued prednisone dosing beyond 10 days would have resulted in a significant increase in induction of metabolism that would cause a clinically significant decrease in DTG exposure.

The literature on the inductive effect of steroids is conflicting, and results vary based on the steroid, dose, duration, and study design. Overall, these drugs are considered weak inducers of CYP3A4. Most studies with dexamethasone, prednisone, or methylprednisolone were not conducted as crossover designs but as case-control-type studies or evaluations of patients, which are confounded by other concomitant medications. In studies evaluating steroid effects on drugs that are metabolized primarily by CYP3A4, steroids generally reduced drug exposure, with decreases in AUC of 11% to 19% for triazolam, 10% for midazolam, 8% for ifosfamide, and 41% for tacrolimus (15, 21–24). However, DTG exposure was not reduced with prednisone, suggesting that the effect of enzyme induction by prednisone on DTG PK is minimal. Even if other glucocorticoids did have an effect on DTG exposure similar to those of the drugs noted above (~10% to 41% reductions in AUC), such modest decreases in the DTG AUC would not result in a dosage change with DTG given the efficacy data from a DTG dose-ranging study demonstrating that doses as low as 10 mg were safe and efficacious in treatment-naive subjects (2).

The coadministration of DTG at 50 mg daily and prednisone at 60 mg daily followed by a 5-day taper was well tolerated in healthy subjects. No deaths, SAEs, or AEs leading to withdrawal occurred, and all AEs were mild. The only drug-related AEs were 3 headache events, including 1 migraine, and abnormal dreams reported by 1 subject during the period before prednisone treatment began.

Because glucocorticoids are weak inducers of CYP3A4, their

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC&lt;sub&gt;0-5&lt;/sub&gt; (µg · h/ml)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/ml)</th>
<th>C&lt;sub&gt;T&lt;/sub&gt; (µg/ml)</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
<th>CL/F (liter/h)</th>
<th>Median T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG</td>
<td>61.3 ± 20.5</td>
<td>4.38 ± 1.0</td>
<td>1.42 ± 0.7</td>
<td>14.1 ± 3.0</td>
<td>0.89 ± 0.27</td>
<td>4.0 (1.0–4.0)</td>
</tr>
<tr>
<td>DTG plus prednisone</td>
<td>70.0 ± 25.8</td>
<td>4.67 ± 1.4</td>
<td>1.74 ± 0.8</td>
<td>15.4 ± 2.8</td>
<td>0.80 ± 0.29</td>
<td>3.5 (1.0–4.0)</td>
</tr>
<tr>
<td>DTG plus prednisone plus taper</td>
<td>68.8 ± 23.5</td>
<td>4.70 ± 1.3</td>
<td>1.69 ± 0.8</td>
<td>15.0 ± 3.6</td>
<td>0.82 ± 0.30</td>
<td>3.5 (1.0–4.0)</td>
</tr>
</tbody>
</table>

*Data are means ± standard deviations (SD), except for median T<sub>max</sub> data, which are means (ranges).

*Pharmacokinetic parameters after 5 days of treatment with DTG (50 mg daily), DTG and prednisone (60 mg daily), or DTG and prednisone followed by 5 days of tapering doses (10-mg taper each day). Values were calculated based on data from 12 subjects for each treatment.
Dolutegravir and Prednisone Interaction

TABLE 3 Statistical analysis of DTG PK parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DTG plus prednisone</th>
<th>DTG plus prednisone</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(day 5) vs DTG*</td>
<td>(day 10) vs DTG*</td>
</tr>
<tr>
<td>AUCl∞,*</td>
<td>1.13 (1.04, 1.21)</td>
<td>1.11 (1.03, 1.20)</td>
</tr>
<tr>
<td>Cmax</td>
<td>1.05 (0.98, 1.12)</td>
<td>1.06 (0.99, 1.14)</td>
</tr>
<tr>
<td>Cmin</td>
<td>1.08 (0.99, 1.17)</td>
<td>1.07 (0.98, 1.16)</td>
</tr>
<tr>
<td>C0</td>
<td>1.21 (1.10, 1.32)</td>
<td>1.17 (1.06, 1.28)</td>
</tr>
<tr>
<td>CL/F</td>
<td>0.89 (0.82, 0.96)</td>
<td>0.90 (0.84, 0.97)</td>
</tr>
<tr>
<td>f1/2</td>
<td>1.11 (1.00, 1.22)</td>
<td>1.07 (0.97, 1.18)</td>
</tr>
</tbody>
</table>

*PK parameters after 5 days of treatment with DTG (50 mg daily) versus DTG and prednisone (60 mg daily). Values were calculated based on data from 12 subjects.

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REFERENCES


