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Pharmacokinetic interactions between buprenorphine/naloxone and tipranavir/ritonavir in HIV-negative subjects chronically receiving buprenorphine/naloxone

R. Douglas Bruce[a,*], Frederick L. Altice[a], David E. Moody[b], Shen-Nan Lin[b], Wenfang B. Fang[b], John P. Sabo[c], Jan M. Wruck[c], Peter J. Piliero[c], Carolyn Conner[c], Laurie Andrews[a], Gerald H. Friedland[a]

[a] Yale University AIDS Program, 135 College Street, Suite 323, New Haven, CT, United States
[b] Center for Human Toxicology, University of Utah, Salt Lake City, UT, United States
[c] Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, United States

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ABSTRACT

HIV-infected patients with opioid dependence often require opioid replacement therapy. Pharmacokinetic interactions between HIV therapy and opioid dependence treatment medications can occur.

HIV-seronegative subjects stabilized on at least 3 weeks of buprenorphine/naloxone (BUP/NLX) therapy sequentially underwent baseline and steady-state pharmacokinetic evaluation of open-label, twice daily tipranavir 500 mg co-administered with ritonavir 200 mg (TPV/r).

Twelve subjects were enrolled and 10 completed the study. Prior to starting TPV/r, the geometric mean BUP $AUC_{0-24\,h}$ and C_{max} were 43.9 ng h/mL and 5.61 ng/mL, respectively. After achieving steady-state with TPV/r (≥7 days), these values were similar at 43.7 ng h/mL and 4.84 ng/mL, respectively. Similar analyses for norBUP, the primary metabolite of BUP, demonstrated a reduction in geometric mean for $AUC_{0-24\,h}$ [68.7–14.7 ng h/mL; ratio = 0.21 (90% CI 0.19–0.25)] and C_{max} [4.75–0.94 ng/mL; ratio = 0.20 (90% CI 0.17–0.23)]. The last measurable NLX concentration (C_{last}) in the concentration–time profile, never measured in previous BUP/NLX interaction studies with antiretroviral medications, was decreased by 20%. Despite these pharmacokinetic effects on BUP metabolites and NLX, no clinical opioid withdrawal symptoms were noted. TPV steady-state $AUC_{0-12\,h}$ and C_{max} decreased 19% and 25%, respectively, and C_{min} was relatively unchanged when compared to historical control subjects receiving TPV/r alone.

No dosage modification of BUP/NLX is required when co-administered with TPV/r. Though mechanistically unclear, it is likely that decreased plasma RTV levels while on BUP/NLX contributed substantially to the decrease in TPV levels. BUP/NLX and TPV/r should therefore be used cautiously to avoid decreased efficacy of TPV in patients taking these agents concomitantly.

1. Introduction

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 (Bruce et al., 2007). Medication-assisted treatment with methadone or buprenorphine (BUP) is one of the evidence-based therapies that have proven to be effective for both primary and secondary HIV prevention (Altice et al., 2006; Kerr et al., 2004) and cost-effective to society (Doran et al., 2003). Moreover, medication-assisted therapy is likely to increase access to and retention on antiretroviral and other therapies (Lucas et al., 2006). BUP, unlike the full opioid-agonist methadone, is a partial *mu*-receptor agonist. This results in a plateau of its agonist effects at higher doses which diminishes the risk of respiratory depression, thereby improving its safety profile compared to methadone (Fiellin and O'Connor, 2002). To reduce diversion, buprenorphine is most commonly prescribed in a sublingual co-formulation with naloxone (NLX). Unlike methadone treatment that is limited in availability and provided only in highly structured treatment settings, BUP can be prescribed by any physician who has completed eight hours of required training and obtained a waiver to prescribe. This potentially allows for the expansion of drug treatment and integration of substance abuse treatment into HIV and other clinical care settings (Basu et al., 2006).

The number of persons eligible for and receiving treatments for both opioid dependence and HIV infection has increased. Co-administration of these therapies, however, has been associated

* Corresponding author. Tel.: +1 203 737 2883.
E-mail address: Robert.bruce@yale.edu (R.D. Bruce).

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with both pharmacokinetic and pharmacodynamic interactions, with important clinical consequences (Bruce and Altice, 2006; Bruce et al., 2006a,b; Spire et al., 2007). The concern about such interactions may deter some patients or providers from initiating potentially life-saving therapy (Lucas et al., 2002). For patients currently on both therapies, real or perceived interactions may reduce therapeutic effectiveness for either or both diseases (Basu et al., 2006). Such interactions may lead to non-adherence with antiretroviral regimens, development of viral resistance, and lack of efficacy of HIV therapy (Bruce et al., 2006a; Lucas et al., 2007). Opioid-dependent patients may also experience adverse effects from HIV treatment that mimic opioid withdrawal and may relapse to using opioids (Altice et al., 1999) or other illicit substances (e.g., cocaine, 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 (Bruce and Altice, 2007).

Tipranavir (TPV), a non-peptidic protease inhibitor used for the treatment of HIV-infected patients resistant to more than one protease inhibitor, has unique pharmacological properties including marked induction of CYP3A4 and UGT1A1. To counteract the induction of CYP3A4 by TPV, it must be co-administered with ritonavir (RTV), a potent inhibitor of CYP3A4. The net effect of co-administration of tipranavir/ritonavir (TPV/r) 500/200 BID is an increase in TPV concentrations to therapeutic levels (Tipranavir Package Insert, 2005; MacGregor et al., 2004; McCallister et al., 2002; Vourvahis and Kashuba, 2007).

BUP is oxidatively metabolized to norbuprenorphine (norBUP) by CYP3A4 and both are glucuronidated (Cone et al., 1984). Because CYP3A4 and UGT1A1 (Bruce et al., 2006b; Chang et al., 2006; King et al., 1996), have primary roles in the metabolic pathway of BUP, the potential exists for pharmacokinetic interactions between BUP and TPV/r, when co-administered. This study was therefore undertaken to ascertain if interactions exist when TPV/r and BUP/NLX are co-administered in individuals receiving chronic BUP/NLX maintenance therapy.

2. Methods

2.1. Study design

This was a multiple dose, open-label, sequential, non-randomized study in BUP-maintained HIV-negative subjects stabilized on at least 3 weeks of BUP/NLX therapy. Subjects were eligible if they were (1) HIV-seronegative; (2) ≥18 years old; (3) not being treated with concomitant medications that might alter drug disposition; (4) without clinically significant medical conditions as determined by medical history, physical examination, ECG, complete blood count, hepatic transaminases, creatinine, and were not pregnant. Urine toxicology was performed at baseline, and repeated prior to conducting drug disposition studies. Urine toxicology screened for amphetamines, benzodiazepines, cocaine, marijuana, methadone, opiates, and oxycodone. Subjects who screened positive for any substance in the urine toxicology were excluded from further evaluation. This study was approved by the Yale University IRB.

Subjects served as their own controls. At baseline, subjects on steady-state BUP/NLX were hospitalized and underwent pharmacokinetic (PK) investigation over a 24-h inpatient period. Blood specimens were drawn at baseline (10 min before BUP/NLX dosing; nominal time 0 h), and at 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, and 24 h after dosing. All subjects were on 16 mg daily of BUP/NLX except for one patient on 24 mg daily.

Subsequently, TPV/r 500 mg/200 mg twice daily was administered for a minimum of seven days under direct observation to insure adherence and to monitor for adverse events. A minimum of 7 days is necessary to achieve steady-state of TPV (Valdez et al., 2004). After achieving TPV steady-state, serial blood samples were collected from each subject over a 24-h inpatient period to determine the plasma drug concentration-time profile of TPV and RTV, and for BUP, norBUP, NLX, and its major metabolite, nornaloxone (norNLX).

Study procedures included standardized measures of opioid withdrawal and opioid excess utilizing the objective opioid withdrawal scale (OOWS), subjective opioid withdrawal scale (SOWS)(Handelsman et al., 1987), and the opioid overdose assessment scale (OOAS) (Friedland et al., 2005). These scales were administered on a daily basis by trained nursing staff prior to the morning dose administration of BUP/NLX and TPV/r. Adverse symptoms were recorded in a standardized manner.

2.2. Bioanalytical procedures

The concentrations of TPV and RTV in heparinized plasma were determined using a validated liquid chromatography–tandem mass spectrometry method at Bioanalytical Systems Inc., West Lafayette, IN. For TPV, accuracy and precision were −5.2% to 4.8% and 1.9% to 7.8%, respectively. For RTV, accuracy and precision were −16.9% to 6.4% and 3.9% to 11.1%, respectively. The lower limit of quantitation for TPV and RTV was 25.0 ng/mL.

The concentrations of BUP, norBUP, NLX and norNLX in heparinized plasma were determined using validated bioanalytical methods at the Center for Human Toxicology, University of Utah, Salt Lake City, UT. All drugs and their metabolites discussed were measured using a validated liquid chromatography–tandem mass spectrometry method. BUP and norBUP were determined as previously described (Moody et al., 2002), the method has a lower limit of quantitation (LLOQ) of 0.1 ng/mL for both analytes. NLX and norNLX were determined using a recently described method (Fang et al., 2009) that uses naltrexone-d_3 and oxymorphone-d_3 as the respective internal standards, solid-phase extraction and has a LLOQ of 0.025 ng/mL for NLX and 0.5 ng/mL for norNLX.

2.3. Pharmacokinetic and statistical analysis

Non-compartmental methods were used for PK analysis (WinNonlin Professional, version 5.2; Pharsight Corporation, Mountain View, CA). C_{max} was defined as the highest observed concentration of a drug in plasma; the corresponding sampling time defined T_{max}. Plasma drug concentrations at 12 h and 24 h after the initial dose were defined as $Cp_{12\,h}$ and $Cp_{24\,h}$. The elimination rate constant (λz) was determined by least-squares linear regression analysis (log concentration versus time) of the last concentration–time points ($n \geq 3$). The $t_{1/2}$ was calculated as $\ln 2/\lambda z$. The area under the plasma drug concentration–time curve (AUC; from 0 h to 24 h [AUC_{0-24}] for BUP, norBUP, NLX and norNLX; and AUC_{0-12} for TPV and RTV) was estimated using the linear-log trapezoidal rule (linear up/log down). Apparent oral clearance (CL/F) was calculated as the drug dose/AUC ratio.

BUP, norBUP, NLX, and norNLX parameters were calculated following sublingual administration of BUP/NLX only and then again following steady-state of TPV/r 500 mg/200 mg twice daily. Statistical analysis was performed with SAS (release 8.2, SAS Institute Inc., Cary, NC). The pharmacokinetic parameters were transformed to the natural logarithm. The difference between the expected means for $\log(T) - \log(R)$ was estimated by the difference in the corresponding Least-Square Means (point estimate) and two-sided 90% confidence intervals based on the t-distribution were computed. These quantities were then back-transformed to the original scale to give the point estimator (geometric mean) and interval estimates for the median intra-subject ratio between response under test and response under reference. Similar analyses were performed for norBUP, NLX and norNLX.

SAS Proc Multtest was used to compare TPV pharmacokinetics in the present study to TPV AUC_{0-12}, C_{max}, and $Cp_{12\,h}$ PK results for 161 healthy volunteers from eight previous clinical studies (Cooper et al., 2005; la Porte et al., 2007a,b; MacGregor et al., 2004; Pham et al., 2008; Sabo et al., 2008; van Heeswijk et al., 2004a,b). Bootstrap arithmetic means (20,000 re-samples) were determined, and the ratios of the means for the test regimen to those for the reference regimen were used to assess the interaction and determine the point estimate. The 5th and 95th percentiles of the distribution of the ratios provided the 90% confidence intervals.

3. Results

3.1. Study disposition

Twenty subjects were screened for this study, with 12 individuals (8 males and 4 females; 8 Caucasian and 4 Black) enrolled. Median (min–max) age, height, weight and body mass index were 44 (21–53) years, 177.8 (165.1–188.0) cm, 75.9 (65.8–112.0) kg, and 25.7 (21.7–35.4) kg/m^2, respectively. Of the 12 subjects treated, two developed adverse events leading to study drug discontinuation before completing the final PK assessment, resulting in 10 evaluable subjects. One subject withdrew due to perioral numbness and lightheadedness likely due to RTV after the first day of study drug administration (Ritonavir package insert, 2007) and one subject withdrew due to elevated hepatic transaminases (>5× ULN; DAIDS Grade 3) detected during routine screening on day 4 which was attributed to known hepatic effects of tipranavir (Tipranavir package insert 2005). All adverse reactions resolved with study drug discontinuation.

3.2. Pharmacokinetic outcomes

The steady-state pharmacokinetics for BUP, norBUP, and NLX in the presence and absence of steady-state TPV/r are summarized in