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Pharmacokinetic Interactions Between Buprenorphine/Naloxone and Once-Daily Lopinavir/Ritonavir

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Abstract

Background—This study was conducted to examine the pharmacokinetic interactions between buprenorphine/naloxone (BUP/NLX) and lopinavir/ritonavir (LPV/r) in HIV-seronegative subjects chronically maintained on BUP/NLX.

Methods—This study was an open labeled pharmacokinetic study in twelve HIV-seronegative subjects stabilized on at least 3 weeks of BUP/NLX therapy. Subjects sequentially underwent baseline and steady-state pharmacokinetic evaluation of once-daily LPV/r (800/200 mg).

Results—Compared to baseline values, BUP AUC0–24h (46.8 vs. 46.2 ng*hr/mL) and Cmax (6.54 vs. 5.88 ng/mL) did not differ significantly after achieving steady-state LPV/r. Similar analyses of norBUP, the primary metabolite of BUP, demonstrated no significant difference in norBUP AUC0–24h (73.7 vs. 52.7 ng*hr/mL); however, Cmax (5.29 vs. 3.11 ng/mL) levels were statistically different ($p<0.05$) after LPV/r administration. Naloxone concentrations were similarly unchanged for AUC0–24h (0.421 vs. 0.374 ng*hr/mL) and Cmax (0.186 vs. 0.186 ng/mL). Using standardized measures, no objective opioid withdrawal was observed. The AUC0–24h and Cmin of LPV in this study did not significantly differ from historical controls (159.6 vs. 171.3 μg*hr/mL) and (2.3 vs. 1.3 μg/mL).

Conclusions—The addition of lopinavir/ritonavir to stabilized patients receiving buprenorphine/naloxone did not affect buprenorphine pharmacokinetics but did increase the clearance of norbuprenorphine. Pharmacodynamic responses indicate that the altered norbuprenorphine clearance did not lead to opioid withdrawal. Buprenorphine/naloxone and lopinavir/ritonavir can be safely co-administered without need for dosage modification.

Keywords

buprenorphine-naloxone; lopinavir; ritonavir; pharmacokinetics; HIV/AIDS; substance abuse

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Introduction

Methadone and buprenorphine (BUP) have had a favorable impact on clinical and public health outcomes of patients with both opioid dependence and HIV/AIDS. BUP, a partial *mu*-receptor agonist, is most commonly prescribed in a co-formulation with naloxone (NLX). Co-administration of HIV and opioid dependence therapies, however, have been associated with pharmacologic medication interactions. These may adversely affect the effectiveness of either or both therapies by producing sub-therapeutic or excessive drug levels, adverse effects, opioid withdrawal or the development of antiretroviral resistance. The occurrence of unrecognized drug interactions may therefore lead to a lack of success of treatment for HIV, opioid dependence, or both.

Lopinavir (LPV), a protease inhibitor, is co-formulated with ritonavir (LPV/r) to inhibit CYP3A4 and increase lopinavir drug levels.[1] Buprenorphine is oxidatively metabolized to norbuprenorphine; both are active agents and are subsequently glucuronidated.[2] Because CYP3A4 has a primary role in the metabolic pathway of buprenorphine,[3] this study was undertaken to ascertain if pharmacologic and pharmacodynamic interactions occur when LPV/r and BUP/NLX are co-administered in individuals receiving chronic BUP/NLX maintenance therapy.

Methods

Study Design

A multiple dose, open-label, sequential, non-randomized pharmacokinetic study was conducted in BUP-maintained HIV-negative subjects stabilized on at least 3 weeks of BUP/NLX therapy. All subjects were maintained on 16 mg of BUP/NLX daily, except for one patient on 24 mg. Subjects served as their own controls. At baseline, subjects on steady-state BUP/NLX were hospitalized and underwent pharmacokinetic investigation over a 24-hour inpatient. Subsequently, LPV/r 800 mg/200 mg once-daily Meltrex tablet formulation was administered for a minimum of ten days under direct daily observation to insure adherence and to achieve LPV steady-state.[4]

Bioanalytical procedures

LPV concentrations in heparinized plasma were measured at the State University of New York using a previously published reverse-phase, high-performance liquid chromatography (HPLC) method.[5] The lower limit of quantiation (LLOQ) was 0.200 μg/mL.

The concentrations of BUP, norBUP, and NLX in heparinized plasma were measured at the University of Utah using a previously published liquid chromatography-tandem mass spectrometry method.[6] The LLOQ for both analytes BUP and nor BUP was 0.1 ng/mL. NLX was determined as recently described with a LLOQ of 0.025 ng/mL.[7]

Pharmacokinetic and Statistical Analysis

Pharmacokinetic parameters were determined by use of non-compartmental methods. The maximum plasma concentration (C_{max}), the plasma concentration at 0 hours (C_0) and24 hours (C_{24}), and the time to maximum plasma concentration (T_{max}) were determinedby

observation of the data. The area under the plasma concentration versus time curve (AUC_{0-X}) was determined by use of the trapezoidal rule. The calculation of the AUC was performed in an Excel spreadsheet (Excel: mac 2001, Microsoft Corp., Richland, WA).

For BUP and NLX data, statistical comparison was made using Student's paired two-sided t-test, except for the nonparametric T_{max}, which was compared using the Wilcoxon's ranked sum test. The mean, standard deviation and N of the results for LPV were compared to those from historical data (group f of Klein et al), [8], by use of unpaired two-sided t-test (Graphpad InStat software for Macintosh version 3.0b, San Diego, CA). Statistical difference was inferred when $p < 0.05$.

Results

Study Subjects

The 12 enrolled subjects included 7 men and 5 women and 7 were Caucasian and 5 were Black. Median (min-max), age, height, weight, body mass index were: 42 (29–54) years, 177.2 (160–185.4) cm, 93.3 (74.3–134.4) kg, and 29.5 (24.6–42.4) kg/m^2, respectively.

Pharmacokinetic Outcomes

The time versus plasma concentration plots of BUP, norBUP, and NLX before and after LPV/r treatment are depicted in Figure 1. The steady-state pharmacokinetics for BUP, norBUP, and NLX in the presence and absence of steady-state LPV/r are summarized in Table 1. BUP AUC_{0-24h} and C_{max} were not statistically different after steady-state LPV. Similar analyses for norBUP demonstrated the nor BUP AUC_{0-24h} was not statistically after steady-state LPV; however, C_{max} was significantly lower ($p< .0.05$) (Table 1). NLX AUC_{0-24h} and C_{max} were not statistically different after the introduction of LPV/r. The NLX T_{max} was significantly decreased from 0.75 (±0.49) to 0.42 (±0.22)) p value) (Table 1). Statistical examination of the results was performed with and without the subject on 24 mg of BUP/NLX. Exclusion of the one patient at 24 mg of BUP/NLX did not change the statistical significance of the results.

LPV AUC_{0-24h} and C_{min} for once-daily dosing in this study were 159.6 ± 60.1 μg hr/mL and 2.3 ± 1.9 μg/mL, respectively. The AUC_{0-24h} and C_{min} were not statistically different between this study and the two sets of historical controls.[8] However, the C_{max} was statistically different between this study and historical controls: 16.5 ± 2.2 μg/mL ($p=<0.0005$) and 14.3 ± 2.6 μg/mL ($p<0.05$).[8]

Clinical Outcomes

No significant clinical or laboratory adverse events occurred. LPV/r administration in BUP/NLX maintained study participants was not associated with opioid withdrawal symptoms as measured by the Objective Opiate Withdrawal Scale (OOWS) and the Subjective Opiate Withdrawal Scale (SOWS).[9]

Discussion

In this open-label pharmacokinetic study examining steady-state BUP/NLX in HIV-seronegative subjects, co-administration of once-daily LPV/r did not statistically affect BUP concentrations. LPV/r co-administration did, however, reduce the plasma concentrations of norBUP, the primary BUP metabolite. The mechanism by which by LPV/r reduces plasma norBUP is unclear. It is known that BUP is metabolized to both norBUP and the hydroxyl-metabolite, M1, by both CYP3A4 and CYP2C8. Subsequent metabolism of norBUP to its hydroxyl-metabolites is only done by CYP3A4. Glucuronidation of both norBUP and BUP are carried out by UGT1A1 and 1A3, while UGT2B17 and 2B7 only glucuronidate BUP. If LPV/r inhibition of BUP metabolism was coupled with induction of UGT1A1 and/or 1A3, the increased glucuronidation could keep both BUP and norbuprenorphine-3-glucuronide concentrations constant, as well as further reduce norBUP. Although norBUP is an active BUP metabolite, it is reported to possess less than 2% of the analgesic potency of BUP and even a significant reduction in norBUP should not clinically compromise the treatment of opioid dependence.[10]

Pharmacokinetic findings were supported by pharmacodynamic data. No symptoms meeting the predetermined definition of withdrawal were documented and no subjects adjusted BUP/NLX dosing or discontinued due to opioid withdrawal.

Because the study design could not include treatment with LPV/r alone, it was not possible to definitively determine the affect of BUP/NLX treatment on the pharmacokinetics of LPV. The study by Klein *et al*, however, provides the most appropriate historical comparison. These historical controls did not have statistically different $AUC_{0–24}$ or C_{min} for LPV, the pharmacokinetic parameters most important in determining therapeutic drug concentrations for protease inhibitors such as LPV/r.[11] As a result, the addition of BUP in the presence of LPV/r should not impact LPV/r's ability to effectively reduce HIV replication.[12] The statistically significant different in C_{max} does not negatively impact the anti-HIV activity of LPV/r and is likely the result of the difficulty in accurately estimating the point of maximal concentration in these subjects. McCance-Katz *et al* studied the interaction of the soft gel capsule of LPV/rm 400mg/100mg twice daily with steady-state BUP.[13] They also found that the main pharmacokinetic changes were related to reduced exposure to norBUP and no opioid withdrawal symptoms were seen. Their direct comparison of separate LPV/r controls to BUP and LPV/r subjects did find that coadministration with BUP significantly increased lopinavir $AUC_{0–12}$ (135 vs. 160 ng·hr/mL). Whether this different response from our finding arose from the different dosing regimen or formulation or other possible causes is yet to be determined.

The results from this study are subject to several limitations. First, the sample size was small, though within the range of similar pharmacological studies. Second, the study design did not allow for within-subject comparison to be made with LPV/r before and after BUP/NLX administration and thus comparison to historical controls was required.

In conclusion, the addition of LPV/r to stabilized patients receiving BUP/NLX did not affect BUP pharmacokinetics but did increase the clearance of norBUP. Pharmacodynamic

responses indicate that the altered norBUP clearance did not lead to opioid withdrawal. It appears that BUP/NLX and LPV/r can be safely co-administered without need for dosage modification. This treatment option holds considerable promise as LPV/r is considered a first-line treatment in resource-rich locales and the most-prescribed second-line antiretroviral treatment globally.

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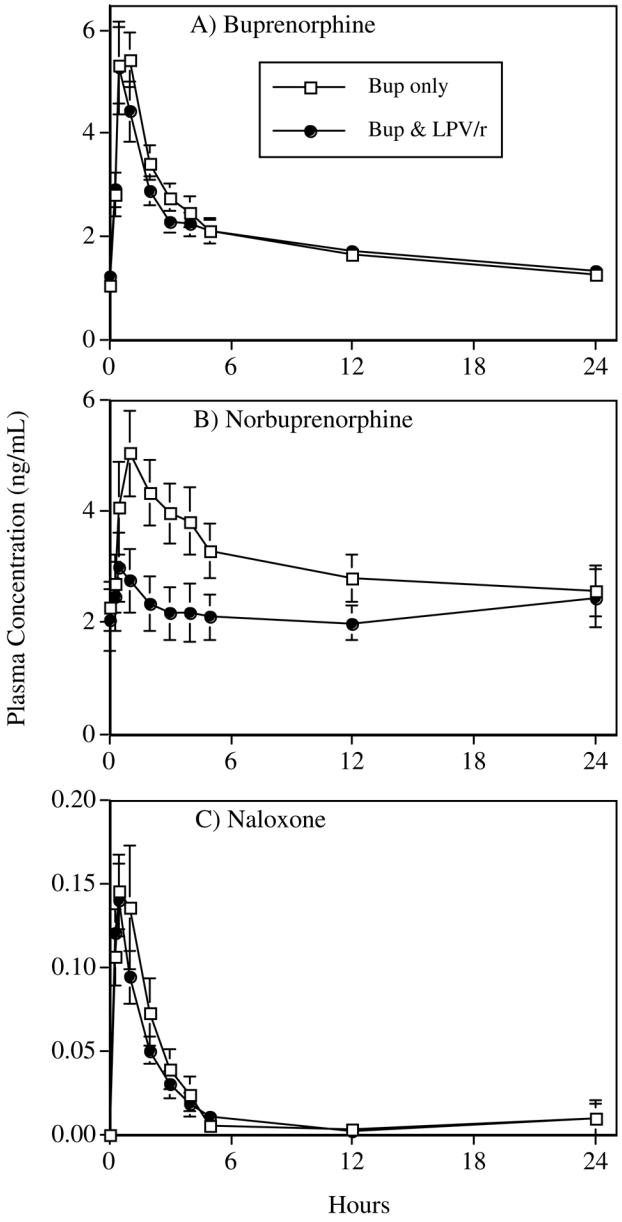

Figure 1.

The time versus plasma concentration plots of BUP, norBUP, and NLX before and after LPVr administration.

Table 1

Pharmacokinetic parameters for subjects on maintenance BUP/NLX alone and plus LPV/r

Analyte / Parameter	Buprenorphine Alone	Buprenorphine & Lopinavir/Ritonavir	p
Buprenorphine			
C_{max} (ng/ml)	6.54 ± 2.31	5.88 ± 2.89	NS
T_{max} (h)	0.79 ± 0.26	1.19 ± 1.34	NS
AUC_{0-24} (ng/ml)(h)	46.8 ± 12.2	46.2 ± 15.3	NS
C_0 (ng/ml)	1.06 ± 0.49	1.21 ± 0.58	NS
C_{24} (ng/ml)	1.24 ± 0.54	1.34 ± 0.59	NS
Norbuprenorphine			
C_{max} (ng/ml)	5.29 ± 2.65	3.11 ± 2.10	< 0.05
T_{max} (h)	1.58 ± 1.00	0.98 ± 1.07	< 0.05
AUC_{0-24} (ng/ml)(h)	73.7 ± 36.8	52.7 ± 34.0	NS
C_0 (ng/ml)	2.28 ± 1.51	2.05 ± 1.96	NS
C_{24} (ng/ml)	2.58 ± 1.60	2.44 ± 1.83	NS
Naloxone			
C_{max} (ng/ml)	0.186 ± 0.127	0.149 ± 0.071	NS
T_{max} (h)	0.75 ± 0.49	0.42 ± 0.22	< 0.05
AUC_{0-24} (ng/ml)(h)	0.421 ± 0.418	0.374 ± 0.342	NS

Values are the mean ± SD for 12 subjects. Statistical comparisons between sessions were made using Student's paired t-test, except for the nonparametric T_{max} where Wilcoxon's ranked sum test was performed.

Table 2

Comparison of LPV/r pharmacokinetic parameters for subjects on maintenance BUP/NLX with historical controls

Parameter	Lopinavir & Buprenorphine Current Study	Lopinavir Alone Historical Control(E)	P	Lopinavir Alone Historical Control (F)	P
N	**12**	**12**		**11**	
AUC (h*μg/ml)	159.6 ± 60.1	199.1 ± 33.9	NS	171.3 ± 46. 6	NS
C_{max} (μg/ml)	11.2 ± 3.7	16.5 ± 2.2	< 0.0005	14.3 ± 2.6	< 0.05
C_{min} (μg/ml)	2.3 ± 1.9	1.6 ± 1.0	NS	1.3 ± 1.2	NS

Historical data are from Klein et al, where two groups (E and F) were treated with LPV/r 800/200 once per day for 10 days.[8] Current data were compared to each separately. Statistical comparisons between groups were made using the two-sided unpaired t-test. NS Not significant ($p \geq 0.05$).