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Interaction between buprenorphine and atazanavir or atazanavir/ritonavir

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Abstract

Opioid addiction and HIV disease frequently co-occur. Adverse drug interactions have been reported between methadone and some HIV medications, but less is known about interactions between buprenorphine, an opioid partial agonist used to treat opioid dependence, and HIV therapeutics. This study examined drug interactions between buprenorphine and the protease inhibitors atazanavir and atazanavir/ritonavir. Opioid-dependent, buprenorphine/naloxone-maintained, HIV-negative volunteers ($n = 10$ per protease inhibitor) participated in two 24-h sessions to determine pharmacokinetics of (1) buprenorphine and (2) buprenorphine and atazanavir (400 mg daily) or atazanavir/ritonavir (300/100 mg daily) following administration for 5 days. Objective opiate withdrawal scale scores and mini-mental state examination were determined prior to and following antiretroviral administration to examine pharmacodynamic effects. Pharmacokinetics of atazanavir and atazanavir/ritonavir were compared in subjects and matched, healthy controls ($n = 10$ per protease inhibitor) to determine effects of buprenorphine. With atazanavir and atazanavir/ritonavir, respectively concentrations of buprenorphine ($p < 0.001$, $p < 0.001$), norbuprenorphine ($p = 0.026$, $p = 0.006$), buprenorphine glucuronide ($p = 0.002$, $p < 0.001$), and norbuprenorphine glucuronide (NS, $p = 0.037$) increased. Buprenorphine treatment did not significantly alter atazanavir or ritonavir concentrations. Three buprenorphine/naloxone-maintained participants reported increased sedation with atazanavir/ritonavir. Atazanavir or atazanavir/ritonavir may increase buprenorphine and buprenorphine metabolite concentrations and might require a decreased buprenorphine dose.

Keywords: Buprenorphine/naloxone; Atazanavir; Ritonavir; Drug interactions

1. Introduction

Injection drug use continues to be a significant risk factor for HIV disease (Deany, 2000). The majority of injection drug users (IDUs) with HIV disease are opioid-dependent and in need of treatment for both HIV disease and substance dependence. Adherence to medical regimens among IDUs is often poor (Arnsten et al., 2002; Mehta et al., 1997). As a result, highly active antiretroviral therapy (HAART) is frequently underutilized in this population because of concerns regarding effective viral suppression (Celentano et al., 2001; Lucas et al., 2001; Strathdee et al., 1998). Treatment for opioid dependence that includes opioid-assisted therapy can promote adherence to HIV disease treatment regimens by stabilizing the chaotic lifestyle of the opioid-addicted individual. Studies have shown that the course of HIV disease in drug users receiving substance abuse treatment is similar to other groups with HIV infection (Cohn, 2002) and the rate of HIV progression can be slowed in IDUs who receive medical intervention (Cohn, 2002; Des Jarlais and Hubbard, 1999).

Methadone has been the most widely used opioid pharmacotherapy for the treatment of opioid dependence. However, its use has been associated with several adverse drug interactions with HIV therapeutics that can produce either elevated methadone concentrations with toxicity, or decreased methadone levels with withdrawal. Both effects may diminish adherence if uncorrected (Altice et al., 1999; McCance-Katz et al., 2002, 2003, 2004; McCance-Katz, 2005). Buprenor-

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phine (BUP) has been shown to be equivalent to methadone in the treatment of opioid-dependent patients (Strain et al., 1996). Buprenorphine/naloxone (BUP/NLX) in a 4:1 ratio is the usual formulation used in the treatment of opioid dependence in the United States [McCance-Katz, 2004]. Naloxone, an opioid antagonist active only when administered parenterally, was added to BUP in a combination tablet to diminish diversion and abuse of the drug by injection (McCance-Katz, 2004). Further, the poor sublingual absorption of naloxone prevents its alteration of BUP opioid agonist effects. To date, BUP has not been shown to produce adverse drug interactions with delavirdine, efavirenz, nelfinavir, ritonavir (RTV) or lopinavir/ritonavir (McCance-Katz et al., 2006a, 2006b).

We now report on the interaction between BUP and a newer protease inhibitor (PI), atazanavir (ATV). Because in clinical practice many PIs are now administered in combination with RTV as a means of boosting PI plasma concentrations and simplifying HAART, a second study in which the interaction of BUP with atazanavir/ritonavir (ATV/r) was determined is also reported.

2. Methods

2.1. Clinical protocol

Forty individuals completed the protocol. Ten BUP/NLX-maintained individuals and 10 non-opioid-maintained participated in each of the ATV and ATV/r studies.

The study was open label and comprised of both (1) a within-subjects component which examined the effect of ATV or ATV/r administration on BUP disposition and (2) a between-subjects component that examined the effect of BUP on the disposition of ATV or ATV/r. Information about the study was available in local mental health centers and substance abuse treatment clinics in Richmond, Virginia, and potential subjects could self-refer. Other participants were recruited from the Richmond community at large through newspaper advertisement and word-of-mouth. Study investigators screened potentially eligible subjects who provided written, voluntary, informed consent following Virginia Commonwealth University Institutional Review Board-approved protocols. Opioid-dependent participants received BUP treatment of their opioid addiction at no charge and were offered monetary compensation for participation in the study protocol. Control participants were offered monetary compensation for their time and effort in the study protocol.

Participants admitted to this study were (1) opioid-dependent individuals treated and stable for at least 2 weeks on standard clinical doses of BUP/NLX (sublingual) daily and (2) a comparison group of age, gender, race and weight-matched, healthy, non-opioid-dependent volunteers. Men and women were enrolled in the study if they were HIV-seronegative by enzyme-linked immunosorbent assay; were 18 years of age or older; were not being treated with medications that might alter hepatic function, and were without clinically significant medical conditions, as determined by medical history, physical examination, ECG, complete blood count, liver function tests (≥3 times the upper limit of normal was exclusionary), glucose, urea nitrogen, creatinine, pregnancy testing (for women) and urinalysis. Urine was also tested for recent use of cocaine, marijuana, opiates, amphetamines, and benzodiazepines; toxicology was repeated prior to conducting drug interaction/drug disposition studies. Participants were tested for HIV viral load in the week before study participation to exclude anyone with recent HIV infection.

Study procedures for opioid-dependent participants included standardized and validated measures of opioid withdrawal by clinician rating (objective opioid withdrawal scale [OOWS], scores ≥3 indicate moderate withdrawal symptoms) (Handelsman et al., 1987) and of cognitive impairment (mini-mental state examination [MMSE] maximum score = 30; scores of <27 indicate cognitive impairment) (Folstein et al., 1975). Adverse symptoms were recorded for all participants using an adverse symptoms checklist that queried for a wide range of adverse experiences including changes in energy, gastrointestinal symptoms, central nervous system effects, genitourinary symptoms, and other somatic complaints scored for severity on an ordinal scale (0–3, with 0 = not present, 1 = mild, 2 = moderate, and 3 = severe, maximum possible score = 87). These ratings were administered at baseline, following stabilization on BUP/NLX (prior to antiretroviral administration), and at completion of the PI dosing period, and for control subjects, prior to and at completion of PI administration.

Subject characteristics are summarized in Table 1. BUP/NLX-maintained subjects met DSM-IV-TR criteria (DSM-IV, 2000) for opioid dependence and were enrolled in the Virginia Commonwealth University Medical Center Buprenorphine Treatment Research program. Other substance use disorders and mental disorders were screened for by clinical assessment and administration of the mini-international neuropsychiatric interview (MINI) (Sheehan et al., 1998).

2.2. Pharmacokinetic study design

Study participants received study medications as outpatients where they reported to the buprenorphine treatment research program and were administered

Table 1
Sample characteristics

	Atazanavir buprenorphine $N = 10$	Atazanavir control $N = 10$	Atazanavir/ritonavir buprenorphine $N = 10$	Atazanavir/ritonavir control $N = 10$
Age (years)	38(2.7)[a]	42(3.1)	37(2.7)	40(3.1)
Weight (kg)	83.4(4.5)	76.0(4.4)	87.6(6.1)	83.7(4.9)
Buprenorphine/naloxone dose (mg/day)	15.2(0.8)/3.8(0.2)	N/A	16.0(0.0)/4.0(0.0)	N/A
Female	3	4	4	3
Race				
African-American	10	8	9	7
Caucasian	–	2	1	3
Substance use disorders				
Opioid dependence	10	–	10	-
Cocaine abuse	8	4	7	3
Cannabis abuse	1	1	2	1
Alcohol abuse	–	1	1	1
IDU	1	0	2	0
Nicotine use (packs/day)	0.6(0.1)	0.5(0.2)	0.7(0.2)	0.6(0.2)
Hepatitis C positive	0	0	1	0

[a] Mean (S.E.).