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The reinforcing and subjective effects of intravenous and intranasal buprenorphine in heroin users

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ABSTRACT

Abuse of buprenorphine (BUP) by the intravenous (IV) route has been documented in several studies, and reports of intranasal (IN) abuse are increasing. However, no studies have directly compared the effects of BUP when it is administered intranasally and intravenously. The present secondary analysis used data from two separate studies to compare the reinforcing and subjective effects of IV and IN buprenorphine. One study evaluated IV buprenorphine (N = 13) and the other evaluated IN buprenorphine (N = 12). Participants were maintained on 2 mg sublingual (SL) BUP and tested with each intranasal or intravenous buprenorphine test dose (0 mg, 2 mg, 4 mg, 8 mg, and 16 mg). During morning laboratory sessions, participants received money (US $20) and sample doses of IN or IV BUP, and then completed subjective effects questionnaires. Later that day, they completed a self-administration task to receive 10% portions of the drug and/or money they previously sampled. In general, positive subjective ratings for both IV and IN BUP were significantly greater than placebo, with IV BUP having a greater effect than IN BUP. All active BUP doses (IV and IN) maintained significantly higher progressive ratio breakpoint values than placebo, but breakpoint values for IV BUP were greater than for IN BUP. Buprenorphine is an effective maintenance treatment for opioid dependence, valued for its ability to reduce the positive subjective effects of other opioids. Nevertheless, the present data demonstrate that in participants maintained on a low dose of SL BUP, the medication itself has abuse liability when used intravenously or intranasally.

1. Introduction

Opioid abuse is a major public health problem in the United States and around the world (SAMHSA, 2010; UNODC, 2012). Maintenance treatment with the partial mu (μ) opioid agonist buprenorphine has been shown to reduce the morbidity and mortality associated with opioid abuse (Mattick et al., 2008). With a superior safety profile in comparison to methadone, buprenorphine treatment quickly gained popularity and the availability of BUP around the world has steadily increased (Auriacombe et al., 2004; Carrieri et al., 2006; Maxwell and McCance-Katz, 2010; Walsh et al., 1994). In spite of its clinical utility, buprenorphine itself has abuse liability and diversion to illicit use has been observed (Johanson et al., 2012).

Originally it was believed that buprenorphine had relatively low abuse liability because of its partial μ agonist profile (Jasinski et al., 1978; Mello and Mendelson, 1985; Walsh et al., 1994, 1995). Yet the abuse of buprenorphine has been noted in Europe (Alho et al., 2007; Auriacombe et al., 2004; Carrieri et al., 2006; Hakansson et al., 2007; Obadia et al., 2001; Roux et al., 2008a,b; Vidal-Trecan et al., 2003), Australia, and South East Asia (Chua and Lee, 2006; Horyniak et al., 2011; Jenkinson et al., 2005; Lee, 2006; Nielsen et al., 2007; Vicknasingam et al., 2010). Consistent with the epidemiological data, laboratory studies have shown that when it is injected (intramuscularly or intravenously) BUP can produce robust opioid-like effects, similar to other potent μ agonists (Bedi et al., 1998; Comer and Collins, 2002; Duke et al., 2010; Strain et al., 1997; Zacny et al., 1997). For example, intramuscular administration of buprenorphine to opioid-dependent participants (maintained on sublingual BUP) produces significant increases in subjective ratings of: drug "liking", "good" drug effect, and "high" (Duke et al., 2010). Similar findings have been reported using intravenously administered buprenorphine in recently detoxified heroin-users (Comer et al., 2005) and buprenorphine-maintained heroin users (Comer et al., 2010).

Although several epidemiological and laboratory studies of injected buprenorphine have been conducted, relatively few studies have examined abuse of buprenorphine by the intranasal route, despite the growing number of reports that the medication is being abused in this manner. For example, studies have reported that the incidence of intranasal BUP abuse is notable in Europe (Hakansson et al., 2007; Roux et al., 2008b). In a rural area of the U.S., a recent investigation on prescription opioid abuse found intranasal buprenorphine abuse to be almost nine

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times more prevalent than intravenous abuse (Young et al., 2010), while another study reported roughly equivalent rates of IV and IN BUP abuse (Nordmann et al., 2012). Only one laboratory study has investigated the pharmacodynamic effects of intranasal buprenorphine (Middleton et al., 2011). These investigators found that in non-dependent, intranasal opioid abusers, IN BUP produced dose-related increases in ratings of drug liking and street value (Middleton et al., 2011). Whether the same profile would be observed in opioid-dependent individuals is unclear, however.

The purpose of the present secondary data analysis was to utilize unpublished data from two separate investigations in order to compare the abuse liability of BUP when it is administered via the IV and IN routes to BUP-dependent heroin users. Employing a same-day sample and choice self-administration procedure, the subjective and reinforcing effects of IV and IN BUP were quantified in order to assess their abuse liability (Comer et al., 2008; Jones and Comer, 2013). In addition, physiological and cognitive responses were also observed. This study may allow us to better understand the differential prevalence of intranasal and intravenous buprenorphine abuse.

2. Methods

2.1. Participants

Participants were required to be physically and mentally healthy intravenous or intranasal heroin users between the ages of 21 and 45 (IV study) or 55 (IN study) years. All participants were required to meet DSM-IV criteria for opioid abuse and physical dependence. Potential participants were excluded from the studies if they were seeking treatment for their drug use, physiologically dependent on alcohol or illicit drugs (other than opioids), or had a severe Axis I psychiatric diagnosis (other than opioid, nicotine or caffeine dependence).

As compensation, participants were paid $25/day with a $25/day bonus for completing the study. In addition to the per diem payment, participants had the opportunity to earn money during the experimental sessions ($20 per sample session plus up to $20 per self-administration session, described below). Following completion of subsequent study procedures, participants were discharged from the hospital, and provided with referrals for drug treatment if they were interested. Opioid detoxification on the inpatient unit was also available to all participants at the end of the studies.

2.2. Procedures

Participants were recruited from the New York City metropolitan area through various print media advertisements. In one study, the effects of IV BUP were evaluated and in a separate study, the effects of IN BUP were examined. Those respondents who met study inclusion/exclusion criteria, based upon the initial telephone interview, were scheduled to come to the New York State Psychiatric Institute for additional screening procedures. Screening consisted of both self-report and clinical interviews administered by a team of research assistants, psychologists, nurses, and physicians. Assessments were made of drug use, medical history and general health (hematology, blood chemistry panel, liver and thyroid functioning, urinalysis, syphilis serology). A semi-structured psychiatric interview and physical examination were performed by a physician. An 11-panel rapid urine drug screen assessed recent use of: amphetamine, barbiturates, benzodiazepines, buprenorphine, cocaine, methadone, methamphetamine, opiates, oxycodone, PCP, and THC. Women were tested for pregnancy by measuring serum hCG levels. Naloxone challenge was used to determine current opioid use in participants who met DSM-IV opioid dependence criteria. In this procedure we administer an intramuscular dose of naloxone (between 0.2 and 0.8 mg) and observe for opioid withdrawal symptoms. Participants also had the option of presenting themselves to clinical staff in a state of opioid withdrawal. Potential participants who were screened for the study were most often excluded for medical or psychiatric concerns.

Once enrolled, participants resided on a locked inpatient unit during the study. During the first week after admission, they were stabilized on 2 mg of sublingual (SL) BUP, which was administered at approximately 8 p.m. The 2 mg dose was chosen in order to prevent withdrawal, but minimize the ability of the sublingual dose to alter the effects of the parenteral dose. During the first week after admission into the hospital, participants were treated for emergent withdrawal symptoms with various supplemental medications until withdrawal symptoms dissipated based on self-report and clinician observations. During the second week after admission into the hospital, while still being maintained on 2 mg SL BUP, each participant was tested with each intranasal **or** intravenous buprenorphine dose in ascending order (2 mg, 4 mg, 8 mg, and 16 mg). One dose was tested on each day, and a placebo (Pbo, 0 mg) dose was randomly inserted into this order. Doses were administered at approximately 11 a.m. during a morning sample session and again at approximately 3 p.m. during an afternoon choice session (see below).

The previously unpublished data presented currently were part of a buprenorphine self-administration "qualification phase." Participants who self-administered more active buprenorphine than placebo qualified for a subsequent series of laboratory sessions that were designed to compare the effects of placebo, buprenorphine, buprenorphine/naloxone, heroin, and naloxone alone. The design of the qualification phases for these two studies was identical, except for the route of buprenorphine administration, and is described in further detail below. Data from the parent IV study have been published (Comer et al., 2010), while the parent IN study is under review. In the present paper, data collected from all participants were included in the analysis regardless of whether they qualified for the parent study.

Qualification phase testing consisted of two types of laboratory sessions, the first of which was conducted approximately 15 h after administration of the SL BUP maintenance dose. During a "**sample" session**, participants received $20 and one of the challenge doses [Placebo (0 mg), BUP 2 mg, 4 mg, 8 mg, 16 mg] administered either intravenously or intranasally. Subjective, performance, and physiological effects were measured before and repeatedly after drug administration. The sample session was followed a few hours later by a self-administration or **"choice" session**. During the choice session, participants were given the opportunity to work for either the dose of drug that was given during the sample session or money. An alternative approach to conducting the sample and choice sessions on the same day would be to complete the choice session on the following day. The investigators opted to complete both sessions on the same day because it more closely mimics the pattern of use on the "street," and our previous experience with the pharmacology of buprenorphine made us confident that carry-over drug effects from the sample to the choice session would be minimal (Comer et al., 2010).

2.2.1. Sample session

At approximately 10 a.m., participants were brought to the laboratory to complete a sample session. Forty minutes (min) prior to drug administration, physiological monitoring began. A pulse oximeter continuously measured arterial oxygen saturation (%SpO_2); heart rate, systolic blood pressure, and diastolic blood pressure were measured every 5 min throughout the session and for an hour following dosing. Participants received money (US $20) and the full doses of the IV or IN challenge drug at 0 min, which occurred at approximately 11 a.m. During the IN study, participants were instructed to insufflate the entire dose within a 30-second period in one or both nostrils, and during the IV study, the entire intravenous solution was infused over the course of 30 seconds. At various time points throughout the session, pupil diameter was measured and participants completed subjective effects batteries and performance tasks (Table 1).