Drug and Alcohol Dependence 179 (2017) 362–369

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Abuse liability of intravenous buprenorphine vs. buprenorphine/naloxone: Importance of absolute naloxone amount

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ARTICLE INFO

Keywords:
Intravenous
Self-administration
Buprenorphine
Opioid
Abuse liability

ABSTRACT

Background: This study sought to determine the relative importance of a range of Bup/Nx doses compared to Bup alone in producing subjective and reinforcing effects.
Methods: Heroin-using volunteers (n = 13) were transitioned onto daily oral hydromorphone (40 mg). Laboratory sessions assessed the reinforcing and subjective effects of intravenous (IV) doses of Bup (1.51, 2.16, 6.15, and 8.64 mg) and Bup/Nx (1.51/0.44, 2.16/0.61, 6.15/1.71, and 8.64/2.44 mg). Placebo (Pbo), heroin (25 mg) and Nx (0.3 mg) were tested as neutral, positive, and negative controls, respectively.
Results: IV Bup alone was self-administered substantially less than IV heroin, though the two largest doses of Bup produced positive subjective effects, drug "Liking" (0–100 mm), which were comparable to heroin (mean difference: Heroin vs Bup 6.15 mg: −3.4 mm, Heroin vs Bup 8.64 mg: −11.3 mm). All indicators of abuse potential seen with IV Bup alone were substantially decreased with the addition of Nx. All Bup/Nx combinations produced ratings of aversive effects, "Bad", which were comparable to, or greater than IV, Nx. On three of the four measures of aversive effects, the largest difference is seen with the 8.64 vs 8.64/2.44 condition.
Conclusions: This study further demonstrates the ability of the Bup/Nx combination to deter IV use. Although none of the Bup/Nx combinations showed indications of abuse potential, formulations with larger absolute Nx, may be less abusable as they precipitate a greater degree of withdrawal.

1. Introduction

Over the past 15 years, sublingual buprenorphine (Bup) maintenance has become one of the most commonly utilized treatments for opioid use disorder (Carrieri et al., 2006; Maxwell and McCance-Katz, 2010). Research has repeatedly shown that Bup maintenance significantly reduces the morbidity and mortality associated with opioid abuse and dependence (Mattick et al., 2008; Stancliff et al., 2013). Although Bup has reduced abuse potential in comparison to opioids that are full μ receptor agonists (Comer et al., 2008; Jasinski et al., 1978; Walsh et al., 1995), administration through rapid routes of administration [intravenous (IV), intramuscular (IM), intranasal (IN)] produces μ agonist-like effects comparable to heroin and oxycodone (Bedi et al., 1998; Comer and Collins, 2002; Comer et al., 2005, 2010; Middleton et al., 2011; Strain et al., 1997; Zacny et al., 1997).

To address concerns of Bup diversion, the opioid antagonist naloxone (Nx) was combined with Bup at a ≈4/1 ratio (Bup/Nx). The addition of Nx, which has very low sublingual/oral bioavailability, is intended to discourage misuse of Bup by parenteral routes by either precipitating withdrawal in dependent individuals or by directly antagonizing the μ agonist effects of Bup (Preston et al., 1990). Several clinical studies have demonstrated that the combined formulation (Bup/Nx) has significantly reduced abuse liability in comparison to Bup alone (Comer et al., 2010; Fudala et al., 1998; Jones et al., 2015; Mendelson et al., 1996, 1999; Stoller et al., 2001).

During early investigations of the effectiveness of this formulation, several studies focused on how varying the relative ratio of Bup to Nx affected its abuse liability (Jones et al., 2015; Mendelson et al., 1999; Preston et al., 1988). Typically, among opioid-dependent volunteers, Bup + Nx combinations produced effects that were qualitatively similar to the effects of Nx alone. Additionally, Nx dose-dependently reduced positive subjective effects, increased aversive effects, and blocked drug self-administration. Combined, this literature indicates that lower Bup/Nx ratios (i.e., larger Nx doses relative to Bup doses) are

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http://dx.doi.org/10.1016/j.drugalcdep.2017.06.033
Received 21 November 2016; Received in revised form 15 June 2017; Accepted 24 June 2017
Available online 26 July 2017

associated with less abuse potential.

Though the importance of the ratio of Bup/Nx has been demonstrated, research has yet to determine how the absolute amounts of Bup and Nx affect their reduced potential for abuse. Post-marketing surveillance has indicated that the introduction of Bup/Nx helped to reduce, but did not eliminate diversion to nonmedical routes of administration (Bruce et al., 2009; Larance et al., 2011, 2014; Lee, 2006; Vicknasingam et al., 2010). Data from these studies indicate that participants may be able to minimize the aversive consequences of IV use through repeated sequential administration of smaller doses (see Yokell et al., 2011 for a review). These data suggest that Bup/Nx formulations with lower absolute Nx content may better lend themselves to this type of diversion. Thus, the purpose of the present study was to assess the reinforcing and subjective effects of various doses of Bup and corresponding doses of Bup/Nx, maintaining the 4/1 ratio.

2. Methods

2.1. Participant selection

Participants were recruited from the New York City metropolitan area through print media advertisements. Screening consisted of: assessments of drug use, general health, and medical history, and laboratory tests (hematology, blood chemistry, and urinalysis). Participants were required to be physically and mentally healthy heroin users between the ages of 21 and 55 years, with previous IV opioid use. All participants were required to meet DSM-5 criteria for opioid use disorder and be physiologically dependent upon opioids. Potential participants were excluded from the study 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 use disorder).

2.2. Design

Participants resided on a locked inpatient unit during the study. During the first 5–7 days after admission, participants were stabilized on oral hydromorphone (HYD) 40 mg/day (10 mg, QID). HYD maintenance was chosen in an effort to model the parameters of a previous investigation demonstrating the utility of the combined Bup/Nx formulations (Stoller et al., 2001). These parameters are also an attempt to model how Bup and Bup/Nx diversion may occur among heroin users. HYD dosing occurred at: 0700 h, 1100 h, 1700 h, and 2100 h on days during which laboratory test sessions did not occur and at: 0700 h, 1315 h, 1700h, and 2100 h on test days.

The IV challenge opioids for this study included doses of Bup alone (1.51, 2.16, 6.15 and 8.64 mg), corresponding doses of Bup/Nx in an ≈4/1 ratio (1.51/0.44, 2.16/0.61, 6.15/1.71, 8.64/2.44 mg), and neutral, positive, and negative controls [placebo (2 ml saline), heroin (25 mg), Nx (0.3 mg), respectively]. This study attempted to model the dosages of two commercially available sublingual buprenorphine products, Suboxone and Zubsolv. The labeled dosage strength of the two products is based on the weight of Bup and Nx free base. In order to avoid potential adverse effects associated with IV administration of the excipients in the commercial products, the active pharmaceutical ingredients (API) of buprenorphine and naloxone were used in the present study. Therefore, in order to calculate the amounts of the API for IV dosing of buprenorphine and naloxone in the current study, we used the following base-to-salt conversion: buprenorphine = 504.1 [hydrochloride (HCL) molecular (Mol) weight (Wt)]/467.6 (Base Mol Wt), Nx = 399.9 (HCl dihydrate Mol Wt)/327.4 (Base Mol Wt). This conversion resulted in the following dose transformations: Zubsolv: 1.4/0.36, 5.7/1.4, (API: 1.51/0.44, 6.15/1.71) and Suboxone: 2/0.5, 8/2 mg (API: 2.16/0.61, 8.64/2.44 mg). This procedure allowed us to make an accurate comparison between the two products via the intravenous route (Fischer et al., 2013). The order of dosing of all IV challenge drugs was randomized, and doses were administered under double-blind conditions.

Table 1
Sample Session Events.

−40	Physiological monitoring (oxygen saturation, blood pressure), Pupil Diameter, Cognitive Effects, Subjective Effects, Withdrawal
0	**Sample IV drug and $20**
5	Pupil Diameter, Subjective Effects, Withdrawal
15	Pupil Diameter, Subjective Effects, Withdrawal
30	Pupil Diameter, Subjective Effects, Withdrawal
45	Pupil Diameter, Subjective Effects, Withdrawal
60	Pupil Diameter, Subjective Effects, Withdrawal
90	Pupil Diameter, Subjective Effects, Withdrawal
105	Pupil Diameter, Subjective Effects, Withdrawal
120	Pupil Diameter, Cognitive Effect, Subjective Effects, Withdrawal
150	Pupil Diameter, Subjective Effects, Withdrawal
180	Pupil Diameter, Subjective Effects, Withdrawal

2.3. Sample and choice self-administration procedure

Testing consisted of two types of laboratory sessions: sample and choice. Sample and choice sessions for each IV challenge dose were completed on sequential days, with at least 24 h between different challenge doses. At approximately 0900 h, participants were brought to the laboratory to complete a sample session. Forty minutes (min) prior to drug administration, physiological monitoring began. At approximately 1000 h, participants received full doses of the IV test drug and money (U.S. $20). Over the course of the next 180 min, participants completed physiological, subjective and performance measures outlined in Table 1.

During the choice session participants completed a self-administration task to receive portions of the dose of drug or money they had sampled the previous day (0–100%, in increments of 10%). Participants could work for all or part of the sampled IV dose or money by choosing the drug or money option that were concurrently available at each trial. Thus, if the dose for that day was 20 mg, at each opportunity participants could respond for 2 mg (10% of 20 mg) or $2 (10% of $20). After a choice was made for one option, participants completed the operant task (finger presses on a computer mouse), which increased independently for each option on the following scale: 50, 100, 200, 400, 800, 1200, 1600, 2000, 2400, and 2800. The primary dependent variable in this choice procedure is the 'break point (BP),' at which responding for the reinforcer stops. At the end of the self-administration task (approximately 1600 h), the participant received whatever (s)he had chosen. Money was added to their study payment, and the IV drug was administered by a study physician.

2.4. Tasks and measures

Subjective Effects: Three questionnaires were used to assess subjective drug effects and opioid withdrawal symptoms. A visual analog scale (VAS) was used to assess subjective and physiological drug effects such as I feel a "Good Effect" and "High". Participants rated each item on the scale from 'Not at all' (0 mm) to 'Extremely' (100 mm). In addition, a 5-item drug effects questionnaire (DEQ) was used to measure drug effects (strength of drug effects, good effects, bad effects, willingness to take the drug again, and drug liking) on a scale of 0 ('No Effect') to 4 ('Very Strong Effect'), or −4 ('Dislike Very Much') to 4 ('Like Very Much'). The Subjective Opioid Withdrawal Scale (SOWS) was used to identify the severity of opioid withdrawal symptoms (Handelsman et al., 1987).

Physiological Measures: Miosis was assessed as a physiological indicator of μ agonist effects using a NeurOptics™ Pupillometer under ambient lighting conditions. For safety, a pulse oximeter continuously monitored oxygen saturation (%SpO2) during sessions, while respiration (breaths per minute), heart rate, and blood pressure (systolic and