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The pharmacodynamic and pharmacokinetic profile of intranasal crushed buprenorphine and buprenorphine/naloxone tablets in opioid abusers

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Abstract

Aims—Sublingual buprenorphine and buprenorphine/naloxone are efficacious opioid dependence pharmacotherapies, but there are reports of their diversion and misuse by the intranasal route. The study objectives were to characterize and compare their intranasal pharmacodynamic and pharmacokinetic profiles.

Design—A randomized, double-blind, placebo-controlled, crossover study.

Setting—An in-patient research unit at the University of Kentucky.

Participants—Healthy adults (n=10) abusing, but not physically dependent on, intranasal opioids.

Measurements—Six sessions (72 hours apart) tested five intranasal doses [0/0, crushed buprenorphine (2, 8 mg), crushed buprenorphine/naloxone (2/0.5, 8/2 mg)] and one intravenous dose (0.8 mg buprenorphine/0.2 mg naloxone for bioavailability assessment). Plasma samples, physiological, subject- and observer-rated measures were collected before and for up to 72 hours after drug administration.

Findings—Both formulations produced time- and dose-dependent increases on subjective and physiological *mu*-opioid agonist effects (e.g. 'liking', miosis). Subjects reported higher subjective ratings and street values for 8 mg compared to 8/2 mg, but these differences were not statistically significant. No significant formulation differences in peak plasma buprenorphine concentration or time-course were observed. Buprenorphine bioavailability was 38–44% and T_{max} was 35–40 minutes after all intranasal doses. Naloxone bioavailability was 24% and 30% following 2/0.5 and 8/2 mg, respectively.

Conclusions—It is difficult to determine if observed differences in abuse potential between intranasal buprenorphine and buprenorphine/naloxone are clinically relevant at the doses tested. Greater bioavailability and faster onset of pharmacodynamic effects compared to sublingual administration suggests a motivation for intranasal misuse in non-dependent opioid abusers. However, significant naloxone absorption from intranasal buprenorphine/naloxone administration

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may deter the likelihood of intranasal misuse of buprenorphine/naloxone, but not buprenorphine, in opioid-dependent individuals.

INTRODUCTION

Buprenorphine, a partial *mu* opioid agonist, is an effective treatment for opioid dependence [1, 2] when administered alone or combined with naloxone. Buprenorphine was first introduced for opioid dependence treatment in 1996 in France [3] and is registered for use in countries across Europe, North America, Asia and in Australia. Food and Drug Administration (FDA) approval of buprenorphine has greatly increased treatment access in the United States where prescriptions for buprenorphine (primarily buprenorphine/naloxone) increased from approximately 267 000 in 2004 to more than 3.3 million in 2008 [4]. Not surprisingly, as availability increased, so have reports of diversion and misuse [5].

Buprenorphine produces a dose-response that is characterized by a ceiling on the magnitude of its pharmacodynamic effects (e.g. respiratory depression; [6–9]) providing a more favorable safety profile than full agonists. However, human laboratory studies demonstrate that buprenorphine has abuse liability, as it can produce euphorigenic effects comparable to full opioid agonists and is self-administered by nondependent opioid users [10, 11]. Because of its lower intrinsic activity and high affinity, buprenorphine may precipitate opioid withdrawal in opioid-dependent individuals, thereby reducing its abuse liability [12–14]. This is supported by epidemiological data indicating that buprenorphine is infrequently (<3%) reported as the drug of choice among prescription opioid-dependent people seeking treatment [15]. The buprenorphine/naloxone combination product was developed to decrease further the abuse potential of buprenorphine and limit its parenteral (i.e., intravenous) diversion. Naloxone is virtually inactive sublingually [16] but, when injected, can precipitate withdrawal [17, 18]. In subjects without physical dependence, there are not clear differences in abuse liability between these formulations [10, 19, 20].

Diversion and misuse of both formulations have been reported. Specifically, buprenorphine and buprenorphine/naloxone tablets are being crushed and then taken by injection [21–23] or intranasally [24–26] in the United States and abroad. While studies have characterized the effects of buprenorphine sublingually and by injection [27–32], no studies, to date, have examined the profile of intranasal (i.e. snorting, inhalation) buprenorphine. The purpose of this study was to examine the intranasal pharmacodynamic and pharmacokinetic profile of crushed buprenorphine and buprenorphine/naloxone in intranasal opioid abusers without opioid physical dependence. The hypotheses were that intranasal buprenorphine/naloxone would have modestly decreased abuse potential compared to buprenorphine alone and that, like other opioids, both buprenorphine and naloxone would exhibit significant intranasal absorption.

METHODS

Subjects

Twelve recreational prescription opioid users were recruited by advertisements and admitted as in-patients. All were in good health according to medical history, physical examination, electrocardiogram and laboratory tests. Exclusion criteria included those with: seizure disorders, history of asthma or respiratory disorders, head injury, hypertension, cardiovascular disease, abnormal electrocardiogram or required daily prescribed medication. All subjects reported illicit opioid use (confirmed by urinalysis during multi-day intake) and intranasal as their preferred administration route. An opioid-negative urine sample was also required during screening in the absence of withdrawal symptoms to exclude opioid physical

dependence. Individuals seeking treatment for substance abuse or successfully sustaining abstinence were excluded.

Two subjects were discharged before study completion for personal reasons or failure to comply with study procedures. Of the ten who completed (seven male, three female), all were Caucasian, with a mean [± standard error of the mean (SEM)] age of 31.2 ± 2.27 years. Subjects reported using illicit opioids 10 ± 2.3 days of the preceding 30 days. Average reported age of first use of illicit opioids was 16 ± 0.9 years with a lifetime history use of opioids of 7.7±1.7 years. Subjects also reported current use of cigarettes (n=9), alcohol (n=10), cocaine (n=6), sedatives/hypnotics/tranquilizers (n=6), marijuana (n=8) and amphetamines (n=1). The University of Kentucky (UK) Institutional Review Board approved this study; all subjects gave written informed consent and were paid for participation. This study was conducted in accordance with the Helsinki guidelines for ethical human research. A Certificate of Confidentiality was obtained from the National Institutes of Health.

Drugs

This study was performed under an investigator-initiated Investigational New Drug Application (#69214) with the FDA. All study medications were stored and prepared in the UK Investigational Pharmacy. Subutex® (2 and 8 mg tablets and matched placebos; all white in color) was obtained through the National Institute on Drug Abuse. Suboxone® (2/0.5 and 8/2 mg tablets and matched placebos; all white in color) was imported from Hull, England (Reckitt Benckiser Pharmaceuticals) because in the United States Suboxone® is orange, which would have broken the subject blind. These doses were selected for testing because they are the currently marketed dose strengths and are available for clinical use and misuse. Individual ampoules containing buprenorphine/naloxone solution (4 mg buprenorphine/1 mg naloxone/1 ml) were obtained through the NIDA drug supply (Murty Pharmaceuticals, Lexington, KY, USA) and diluted 1:5 for a final dose of 0.8 mg buprenorphine/0.2 mg naloxone/1 ml for intravenous administration. Intravenous doses of both drugs were included primarily to assess bioavailability. The intravenous naloxone dose was selected because 0.2 mg naloxone is sufficient to precipitate withdrawal in opioid dependent individuals; thus, the expected plasma concentrations would be clinically informative and relevant. The intravenous buprenorphine dose was selected to maintain the 4:1 ratio of buprenorphine and naloxone used in the marketed medication.

Study Design

This 3.5 week in-patient study employed a randomized, double-blind, within-subject, placebo-controlled design. It was conducted at the Clinical Research Development and Operations Center (CR DOC), a research unit in the UK hospital. Subjects participated in six 6.5-hour experimental sessions scheduled minimally 72 hours apart.

Experimental Sessions

Following admission, subjects were familiarized with and trained on all procedures. Subjects were maintained on a caffeine-free diet, allowed a light breakfast 2 hours before session, and could smoke up to 30 minutes before session. Females were tested weekly for pregnancy with no positive results. On session days, subjects received powder from crushed placebo, buprenorphine (2 or 8 mg) or buprenorphine/naloxone (2/0.5 or 8/2 mg) tablets of equivalent volume (100 mg). The placebo dose contained powder from the matched placebo tablets of both buprenorphine (50%) and buprenorphine/naloxone (50%). Subjects transferred the powder to a mirror, split the powder into two lines, and snorted one line through each nostril using a straw. Subjects completed computerized questionnaires using a keyboard and/or mouse. A trained research assistant used a keyboard to initiate tasks and to enter observer-

rated measures. Baseline data were collected for 30 minutes prior and 6 hours after drug administration (at 0900). Table 1 details the timing of all pharmacodynamic measures.

Subject and Observer-Rated Measures

Subject-rated measures included: six visual analog scales (VAS) rated from 0 ('not at all') – 100 ('extremely'; [33]); the Addiction Research Center Inventory (ARCI) short form [34]; street value questionnaire; a 25-item adjective checklist that encompassed both an Agonist scale and mixed Agonist-Antagonist scale [16, 35]; and an observer-rated opioid adjective rating scale.

Subjects also completed two locally developed questionnaires to characterize the sensations related to nasal inhalation of the test drugs using a 5-point Likert scale: (i) 'When I snorted this drug it tasted or smelled…' sweet, salty, sour, bitter, like metal, like medicine, like chalk, like fruit, bad, good; and (ii) 'When I snorted this drug, my nose or throat felt…' burning, tingling, itching, pain, congestion, numbness, stinging, thirsty, dry mouth. This second questionnaire also included a 'yes' or 'no' question 'Was it difficult to snort the amount of powder provided?'

Performance and Ocular Tasks

The digit symbol substitution task (DSST) was used to measure information processing [36]. The Maddox-Wing test (Model CE0120, Clement Clarke Ltd., London, UK) was used to assess ocular exophoria or under convergence [33].

Physiological Measures

Oxygen saturation, heart rate and blood pressure were collected every min using a Dinamap Non-Invasive Patient Monitor (GE Medical Systems, Tampa, FL) for 30 minutes before and for 6 hours after drug administration. Respiratory rate was determined by counting the number of breaths within 30 seconds and multiplying by 2. Pupil diameter was determined using a pupillometer (NeurOptics, San Clemente, CA) in constant lighting conditions.

Blood Sample Collection and Pharmacokinetic Analysis

Intravenous catheter(s) were placed into the antecubital vein(s) prior to the start of session, one for intranasal sessions and two (in separate arms) for the intravenous session (the second for drug administration). Catheters remained in place for up to 72 hours and were flushed regularly to maintain patency. Blood samples (7 ml/sample) were collected into two 4-ml green heparinized vacutainers for determination of buprenorphine, norbuprenorphine, buprenorphine-3-glucuronide, norbuprenorphine-3-glucuronide and naloxone levels. Samples were collected at baseline and 5, 10, 15, 20, 30, 45 minutes, 1, 2, 4, 8, 12, 24, 48 and 72 hours post-drug administration and one sample at 2 minutes during the intravenous session. Vacutainers were inverted 8–10 times and centrifuged (3000 ***g*** × 15 minutes) immediately to prevent hemolysis. Plasma was transferred to a vial, stored at −80°C, shipped to the University of Utah Center for Human Toxicology and assayed for buprenorphine (and metabolites) and naloxone (the latter only for those sessions testing buprenorphine/naloxone). Analysis was performed as previously described [37]. This technique reliably quantifies buprenorphine (and metabolites) and naloxone levels with a lower limit of quantitation (LLOQ) of 0.1 ng/ml and 0.025 ng/ml, respectively.

Statistical Analysis

All measures were analyzed as raw time-course data with two-factor within-subject analysis of variance [ANOVA; dose (five levels) × time (intervals in Table 1)] followed by Tukey *post-hoc* analyses. Physiological measures collected every minute were first averaged across

time to yield intervals (5–30 minutes) corresponding to collection of subjective reports. Peak scores (minimum or maximum depending upon the *a priori* predicted direction of effect) were derived from time-course data and analyzed using one-factor ANOVA for dose. Planned comparisons with Bonferroni corrections were used for active dose comparisons to placebo and between formulations.

Buprenorphine concentrations were analyzed using 3-factor ANOVA [dose (two levels) by formulation (two levels) by time]. Naloxone concentrations were analyzed for 8 hours after buprenorphine/naloxone with two-factor ANOVA [dose (two levels) × time]. Plasma area-under-the-curve (AUC) was calculated by the trapezoidal rule (0–72 hours). Mean maximum concentrations (C_{max}) and time-to-maximum concentrations (T_{max}) were calculated for buprenorphine, its metabolites, and naloxone. Observed absolute bioavailability (F_{obs}) of intranasal buprenorphine and naloxone was determined as follows: F_{obs} = (AUC intranasal/AUC intravenous) × (dose intravenous/dose intranasal). Values below the LLOQ were scored as zero for mean concentrations and AUC calculations. The elimination rate constant (λz) was estimated by linear regression from a natural log linear plot of data from 12, 24 and 48 hours for 8 and 8/2 mg buprenorphine and data from 45 minutes, 1, 2 and 4 hours naloxone (the terminal post-distribution phases). Buprenorphine concentrations below the LLOQ at these times or with a slope approaching 0 for these time points were excluded from the λz calculation. For low doses of buprenorphine and all buprenorphine metabolites, λz was not calculated due to insufficient concentrations at these times. The terminal half-life ($t_{1/2}$) was calculated as 0.693/ λz. One-factor ANOVA along with Tukey tests were used to determine differences among the buprenorphine parent and metabolite conditions on pharmacokinetic parameters. Paired *t*-tests were used to compare pharmacokinetic parameters for naloxone. All ANOVA models were run with SAS 9.1 Proc Mixed software for Windows and were considered significant when $P < 0.05$.

RESULTS

Physiological Measures

Figure 1 illustrates the time-course for pupil diameter over the first 72 hours after intranasal dosing. There were significant effects of dose and time (see figure legend for statistical outcomes). Significant miosis was observed within 30 minutes of dosing after 8 and 8/2 mg, but not until 45 minutes for the lower doses (2 and 2/0.5 mg; Tukey test $P < 0.05$). Data from the first hour reveal a slightly earlier onset for buprenorphine alone compared to the same doses of the combination; however, these were not significant. Tukey *post-hoc* analyses revealed that miosis lasted for up to 6 hours for the low doses (2 and 2/0.5 mg), but was still evident 24 hours after administration of 8 and 8/2 mg. Similarly, peak analysis of minimum diameter scores revealed a main effect of dose (Table 2) with all active doses significantly different from placebo ($P < 0.0001$; planned comparisons).

Figure 2 illustrates the time-course for oxygen saturation over the first 6 hours after intranasal dosing. There were significant effects of dose and time (see figure legend for statistics). While all active doses decreased oxygen saturation compared to placebo, Tukey *post-hoc* analyses revealed significant differences for only the 8 mg dose that occurred after peak effect was reached (1.5 – 4 hours). Peak analyses revealed significant dose effects and planned comparisons revealed a reduction in oxygen saturation for all active doses compared to placebo ($P < 0.05$; Table 2). Similarly, there was a significant effect of dose on respiratory rate for both time-course and peak analysis (see Table 2) with the 8, 2/0.5 and 8/2 mg doses significantly decreased compared to placebo ($P < 0.05$; planned comparisons). Time-course analyses revealed no significant dose effects for heart rate, systolic or diastolic blood pressure. However, planned comparisons revealed that the peak increase in systolic

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