Effects of buprenorphine and naloxone in morphine-stabilized opioid addicts

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Abstract

The present study, conducted as part of the development of a buprenorphine/naloxone combination product, was designed to evaluate the individual and combined effects of intravenously administered buprenorphine and naloxone. This in-patient trial used a randomized, double-blind, crossover design. Ten opioid-dependent male subjects were stabilized and maintained on morphine, 15 mg given intramuscularly four times daily. Then, at 48- to 72-h intervals, subjects received one of the following by intravenous injection: (1) placebo, (2) morphine 15 mg, (3) buprenorphine 2 mg, (4) buprenorphine 2 mg/naloxone 0.5 mg, and (5) naloxone 0.5 mg. Both naloxone and buprenorphine/naloxone produced significant ($P < 0.005$) opioid withdrawal effects compared to placebo as assessed with the CINA scale, an instrument which utilizes subject- and observer-reported, as well as physiological parameters. The combination of buprenorphine with naloxone in a 4:1 ratio produced opioid antagonist-like effects which should limit its potential for intravenous abuse by opioid addicts. © 1998 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Buprenorphine, a mu-opioid partial agonist, is currently under development as a pharmacotherapy for opioid dependence. However, buprenorphine itself may have the potential for abuse. The administration of buprenorphine has been associated with opioid-like effects (Heel et al., 1979; Lewis, 1985; Mello and Mendelson, 1985; Pickworth et al., 1993; Bickel and Amass, 1995) and the abuse of buprenorphine by the parenteral route has been reported in a number of areas, including Europe, India, and New Zealand (Rainey, 1986; O’Connor et al., 1988; Chowdhury and Chowdhury, 1990; San et al., 1992; Forsyth et al., 1993).

One promising approach to minimize potential abuse and diversion is the combination of buprenorphine with the short-acting opioid antagonist naloxone. In an effort to develop a dosage form suitable for general use, and in consideration of the poor oral bioavailability of buprenorphine (Jasinski et al., 1981), a combination product containing buprenorphine and naloxone for sublingual administration is currently under development (Hawks and Chiang, 1995). Naloxone is being evaluated for such a combination product because of its low sublingual bioavailability compared to that for buprenorphine. While the parenteral to sublingual potency ratio for naloxone has not been precisely determined, it has been estimated to be approximately 10–20:1 from clinical pharmacology studies of opioid-dependent individuals (Preston et al., 1990). For

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1 Some of the results from this study were presented at the 97th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, Lake Buena Vista, FL, 22 March 1996.
buprenorphine, however, this relative potency ratio has been reported to be approximately 1.5–3:1 (Olley and Tong, 1988; Jasinski et al., 1989; Moa and Zetterstrom, 1990). Thus, it would be expected that an appropriately formulated combination product would be undesirable for parenteral abuse by opioid-dependent individuals (due to the presence of naloxone), but safe and effective when administered sublingually as an opioid-dependence treatment agent (because of the limited sublingual bioavailability of naloxone).

Naloxone has previously been used in the formulation of opioid analgesics (e.g. pentazocine, buprenorphine, and tildidine) in order to reduce their abuse potential, and the effects of a combination of buprenorphine and naloxone given parenterally at dose ratios ranging from 8:1 to 1:2 have been investigated in both opioid-dependent and non-dependent individuals (Preston et al., 1988; Weinhold et al., 1992; Jones and Mendelson, 1996; Mendelson et al., 1996). The data showed dose-dependent opioid antagonist effects, with higher ratios of naloxone in the combination being associated with greater antagonist effects in dependent individuals. From the available data, it appeared that an 8:1 ratio of buprenorphine to naloxone could be sufficient to produce clinically significant opioid antagonist effects in some opioid dependent individuals, while ratios of 2:1 or less would be likely to produce these effects in most individuals. The 4:1 ratio was chosen in the present study since preliminary data indicated that this ratio could provide the desired opioid antagonist effects if abused, while allowing the amount of naloxone in the product, relative to buprenorphine, to be kept to a minimum.

The present study differed in a number of ways from previous trials assessing the effects of buprenorphine and naloxone combinations. For example, one early trial utilized lower, analgesic doses of buprenorphine (administered subcutaneously) in methadone-maintained individuals (Preston et al., 1988). Other trials have included subjects not currently dependent on opioids given the combination intramuscularly (Weinhold et al., 1992); a lower buprenorphine to naloxone ratio in heroin-addicted individuals (Mendelson et al., 1996); or no concurrent naloxone-only challenge treatment (Jones and Mendelson, 1996). These differences do not represent shortcomings of earlier trials, but rather give an indication of how studies conducted thus far, including the present one, have provided information relevant to the effects of buprenorphine/naloxone combinations in various subject populations under varying experimental conditions.

The importance of assessing the effects of buprenorphine and naloxone in subjects abusing, or maintained on, various opioids is underscored by pharmacodynamic and pharmacological differences between commonly used and/or abused opioid drugs. These differences may be influenced by the drugs’ route of administration and pharmacokinetic profile. For example, utilizing equipotent doses of heroin and morphine, Martin and Fraser (1961) observed that the heroin abstinence syndrome was brief, and of shorter duration than that of morphine. Conversely, the association of methadone with a protracted abstinence syndrome had been observed as early as 1948 (Isbell et al., 1948). Additionally, the time course of naloxone-precipitated withdrawal effects in individuals administered methadone acutely has been reported to be four to seven times longer than that observed following acute morphine administration (Nutt and Jasinski, 1974; Bickel et al., 1988a; Heishman et al., 1989; Kirby et al., 1990; Stitzer et al., 1991; Wright et al., 1991). Naloxone has been shown to produce more variable responses in individuals taking street opiates compared to methadone-maintenance patients (Preston et al., 1990), and buprenorphine itself has been shown to produce variable effects in individuals maintained on methadone (Strain et al., 1992, 1995; Walsh et al., 1995) as compared to those taking ‘street’ opiates (Mendelson et al., 1996) or morphine (Schuh et al., 1996).

The purpose of this study was to evaluate the behavioral and physiological effects of buprenorphine and naloxone, both alone and in combination, in opioid addicts stabilized on a common dosage of morphine. The present investigation, and two others (Jones and Mendelson, 1996; Mendelson et al., 1996), were conducted to assess the effects of various buprenorphine:naloxone dosage ratios in both heroin-dependent and morphine-stabilized individuals prior to the initiation of a multisite efficacy/safety evaluation of a buprenorphine/naloxone combination product. It was hypothesized that a buprenorphine and naloxone combination at a dosage ratio of 4:1 would be associated with measurable precipitated opioid withdrawal signs and symptoms and/or changes in the magnitude of buprenorphine agonist effects when the combination was given intravenously.

2. Subjects and methods

This study was conducted using a double-blind, placebo-controlled, randomized, crossover design (two 5 × 5 Latin squares). It had a per-subject duration of 14 to 18 days and was conducted over a period of 6 months. A total of 10 opioid-dependent veterans, seeking opioid substitution or detoxification treatment, were enrolled. Prior to entering the study, all potential subjects received a physical examination, including an electrocardiogram, psychiatric evaluation, routine blood chemistry, and hepatitis B screen. The eligibility of individuals for study participation was evaluated based on the following criteria:
2.1. Inclusion criteria

(1) Male or female veteran, 18–59 years of age (inclusive); (2) Current dependence on heroin, morphine, or hydromorphone according to DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, 1987) criteria; (3) Self-reported use of one or more of the opioids listed in (2) above for at least 21 of the past 30 days, with self-reported use for at least the past 6 months; (4) Urine toxicology screen positive for opioids and negative for methadone at the time of screening; (5) No active illness as determined by history, physical examination, electrocardiogram, and clinical laboratory tests; and (6) Weight within 15% of ideal body weight according to current actuarial tables.

2.2. Exclusion criteria

(1) Current dependence on any psychoactive substance other than opioids, caffeine, or nicotine; (2) Self-reported use of methadone, buprenorphine, or methadyl acetate in the past 30 days; (3) Active neurological or psychiatric disorders which could make study compliance or participation difficult; (4) Significant cardiovascular, hepatic, or renal disease; (5) Participation in an investigational drug or device study within 30 days of entering the current study; and (6) Females who are pregnant, or who are of childbearing potential and are not using a medically acceptable method of birth control.

Subjects were reimbursed for their time at the rate of $10 per day. Following completion of the study protocol, subjects were offered a standard outpatient methadone detoxification or methadone maintenance treatment, as appropriate. The study was conducted on the in-patient Substance Abuse Treatment Unit of the Department of Veterans Affairs Medical Center, Philadelphia, and was approved by the Human Subjects Subcommittee of that institution.

Upon admission to the inpatient unit (study day 1), subjects were stabilized on morphine sulfate 15 mg intramuscularly given two to four times daily, depending on individual response and time of admission. On study day 2, subjects received morphine sulfate 15 mg intramuscularly given three to four times daily depending on individual response. Thereafter, and through to the completion of the study, subjects were maintained on morphine sulfate 15 mg intramuscularly given four times daily (at approximately 6 a.m., 11 a.m., 4:30 p.m., and 10 p.m.). On the last in-patient day, prior to discharge, subjects received methadone, 30 mg orally, in place of morphine, and were enrolled in the outpatient methadone treatment program at the Department of Veterans Affairs Medical Center (Philadelphia) on the day of discharge.

Throughout the course of the study, at 48- to 72-h intervals, subjects were administered one of the following challenge treatments intravenously at 10 a.m.: (A) placebo; (B) morphine sulfate 15 mg; (C) buprenorphine hydrochloride 2 mg; (D) buprenorphine hydrochloride 2 mg/naloxone hydrochloride 0.5 mg; and (E) naloxone hydrochloride 0.5 mg. These intervals were chosen to allow the acute effects of the challenge drugs to fully dissipate between treatments, and to allow the challenges to be administered on a Monday/Wednesday/Friday schedule. Challenge treatments were administered over a period of 1 min. They were given intravenously since this is expected to be the preferred route of potential abuse of the combination product by individuals who regularly abuse opioids intravenously.

Morphine sulfate given intramuscularly was obtained from Wyeth-Ayerst, Philadelphia, PA and administered in a volume of 1 ml; morphine sulfate given intravenously was obtained from Elkins–Sinn, Cherry Hill, NJ. Both morphine solutions were supplied in concentrations of 15 mg/ml. Naloxone hydrochloride for injection (2 mg/ml) and buprenorphine hydrochloride (2 mg/ml) were supplied by the National Institute on Drug Abuse, Medications Development Division; no further preparation of the solutions was required. Placebo consisted of normal saline for injection.

Before and after the administration of the challenge treatments, subjects were evaluated for the presence of opioid agonist and antagonist effects using behavioral and physiological scales and assessments. These scales and assessments, and the times they were administered relative to the challenge drug are as follows:

<table>
<thead>
<tr>
<th>Time</th>
<th>CINA, AEC</th>
<th>VAS-B, AEC, G, SPEND</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
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<td>VAS-G, SPEND</td>
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<td>+5 min</td>
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</tr>
<tr>
<td>+60 min</td>
<td>CINA, VAS-B, AEC,</td>
<td>VAS-G, SPEND</td>
</tr>
</tbody>
</table>

The CINA (Clinical Institute Narcotic Assessment Scale (Peachey and Lei, 1988)) is a 13-item (nausea/vomiting, abdominal complaints, feeling hot or cold, muscle aches, gooseflesh, sweating, restlessness, tremor, lacrimation, nasal congestion, yawning, heart rate, systolic blood pressure) opioid withdrawal assessment scale. The scale incorporates subject-reported symptoms (the first four items listed above), observer-rated signs (the next seven items), and physiologic assessments (the last two items). VAS-B and VAS-G are 100
Table 1
Subject demographic data

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Race</th>
<th>Age of first heroin use (approximate)</th>
<th>Heroin usage pattern at time of enrollment</th>
<th>Height (in)</th>
<th>Weight (lbs)</th>
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<td>166</td>
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<tr>
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<td>67</td>
<td>160</td>
</tr>
</tbody>
</table>

mm visual analog scales assessing subject-reported ‘bad’ and ‘good’ drug effects, respectively. Each is anchored with the terms ‘none’ on the zero end and ‘the most ever’ on the 100 mm end. The AEC (Agonist Effects Checklist) is a 20-item, subject-completed checklist consisting of terms or phrases typical of opioid agonist effects. The checklist used in the present study differed from the one previously utilized and reported on by Bickel and colleagues (Bickel et al., 1988b) only by the substitution of the word ‘nausea’ for the term ‘turning of stomach’. SPEND was an open-ended question: ‘How much would you spend for the challenge drug right now’?

2.3. Analytical methods

The study was analyzed as a five-period crossover design with each subject receiving one of the five intravenous challenge drugs at each of the five time periods. The analyses were performed using a replicated Latin square model. Natural log (or natural log + 1) transformations of the data were performed as required to correct for non-normality. Following the finding of a significant main effect at $\alpha = 0.05$, pairwise comparisons with Bonferroni adjustments were performed. This conservative statistical approach was chosen to minimize the potential for a Type 1 error. Thus, for each pairwise treatment mean comparison, statistical significance was declared at $\alpha = 0.005$ ($0.05/10$ comparisons $= 0.005$).

For the CINA scale, comparisons were made with respect to total scores calculated at the cumulative + 25 and + 60 min post-challenge time points. The method of cumulative, rather than individual time-point scoring, was chosen to preserve the original scoring procedure utilized by the scale’s developers (Peachey and Lei, 1988). For the VAS-G and VAS-B, data were analyzed with respect to peak mean scores and area under-the-curve (AUC). AUCs were calculated using the trapezoidal rule. For the AEC, peak mean and AUC scores corrected for baseline (− 10-min observation) were analyzed. For SPEND, peak mean scores were analyzed using a 2 (yes/no) by 5 (each challenge drug condition) Fisher’s exact test with regard to whether subjects reported that they would have spent $S5 or more. While it was initially planned to analyze the SPEND data using parametric methods (i.e. considering SPEND as a continuous variable), 72% of subjects’ responses were '$0' with the majority of the remainder being $S1, $S5, $S10, or $S20, thus making a parametric analysis inappropriate and potentially misleading.

For three of the analyses (peak mean VAS-G, peak mean VAS-B, and AUC VAS-B), the respective data were found not to be normally distributed even following transformation. The replicated Latin square design presents a complex variance structure which can not be accommodated with nonparametric techniques. Therefore, analyses were performed using a Friedman’s two-factor (subjects, treatment) analysis of variance (ANOVA). Subsequent to a significant ANOVA, pairwise comparisons were performed on the average ranks for each of the treatments.

3. Results

Eighteen subjects signed consent forms for participation and were enrolled into the protocol; all were male and ten completed the study (demographic data shown in Table 1). Six of the eight non-completers were determined to be ineligible for participation during the screening phase based on the inclusion/exclusion criteria, and two individuals discontinued participation in the study following enrolment citing ‘personal reasons’. Nine of the ten subjects who completed the protocol entered an opioid detoxification program following discharge from the study; one entered methadone maintenance.
Both naloxone and the buprenorphine/naloxone combination were associated with significant withdrawal effects compared to placebo as assessed by the CINA scale measured over both the first 25 (CINA-25) and first 60 min (CINA-60) following challenge drug administration (Fig. 1). As this scale provides a cumulative assessment over time, scores were necessarily higher for the longer observation period. Still, the order of treatments, from highest to lowest scale scores, was the same (naloxone > buprenorphine/naloxone > morphine > buprenorphine > placebo) for both measurement intervals. The effects produced by naloxone were not significantly greater than those produced by the buprenorphine/naloxone combination.

Naloxone produced significant ‘bad drug effects’ compared to each of the other treatments as assessed by peak mean scores on a 100 mm visual analog scale (Fig. 2, bottom panel). For naloxone, the highest mean score was observed at 45 min post drug administration. Practically, however, all mean scores following naloxone administration were appreciably elevated with regards to those following placebo administration. With respect to AUC scores, naloxone was associated with significantly greater effects than placebo. The difference between the buprenorphine/naloxone combination and placebo approached significance (P = 0.0057) considering the conservative Bonferroni correction applied.
Neither morphine nor buprenorphine (nor any other challenge drug) was associated with significant effects on the agonist effects checklist assessing typical opioid-like effects. The overall challenge drug effect was not significant.

Similarly, no challenge drug produced significant ‘good effects’ compared to placebo as assessed by peak mean scores on a 100 mm visual analog scale (Fig. 2, top panel). However, morphine produced significant ‘good effects’ with respect to AUC scores compared to both placebo and buprenorphine.

There was a significant difference between groups when subjects were asked about the amount of money they would spend for the challenge drug. Eight of the ten subjects reported that would spend $5 or more for the morphine injection. Only two of ten subjects reported that they would spend $5 or more for any of the other active treatments. All subjects reported that they would spend $0 for a naloxone injection.

4. Discussion

The present study examined the effects of intravenous buprenorphine (2 mg) and naloxone (0.5 mg) given alone and in combination to individuals maintained on intramuscular morphine, 60 mg per day (15 mg four times daily). This amount of morphine is approximately equivalent to 30 mg of oral methadone with respect to its capacity to suppress opioid withdrawal signs and symptoms in opioid-dependent individuals (Jasinski et al., 1977). Findings from the present study extend and complement those from previous studies assessing the potential for naloxone to alter the abuse liability of buprenorphine.

In an earlier study (Preston et al., 1988) that utilized analgesic doses of buprenorphine, buprenorphine and naloxone (0.2 mg) combinations, at dosage ratios of 1:1 and 1.5:1 given subcutaneously, were noted to precipitate a withdrawal syndrome in opioid-dependent volunteers maintained on 30 mg of methadone daily. Buprenorphine alone had no significant effects in that study population, and the buprenorphine/naloxone combination produced a profile of effects similar to that produced by naloxone alone. These data suggested that such a combination of medications would have a low abuse potential in methadone-maintained individuals. In a subsequent study (Strain et al., 1992) with a similar subject group, buprenorphine given alone in intramuscular doses of up to 8 mg was associated with no systematic, significant opioid agonist or antagonist effects, while the administration of 0.1 and 0.2 mg of intramuscular naloxone was associated with a characteristic antagonist response.

Aside from studies evaluating the analgesic effectiveness of the medication combination, most studies assessing the combined effects of buprenorphine and naloxone have considered methadone-maintained individuals (as noted above) or non-dependent opioid abusers (Weinhold et al., 1992). However, few (Jones and Mendelson, 1996; Mendelson et al., 1996) including the present study, have examined the effects of buprenorphine/naloxone combinations in individuals currently dependent on heroin or morphine.

In the present study, only morphine was associated with significant effects (AUC scores) on a scale assessing ‘good’ drug effects, or one on which subjects were asked the amount of money they would spend for the challenge drug. Neither buprenorphine nor the buprenorphine/naloxone combination was associated with such positive effects. In another investigation (Mendelson et al., 1996), the same dose of buprenorphine (2 mg administered intravenously) given to heroin-dependent individuals was associated with opioid agonist effects. Numerous factors may account for this difference between the two studies, including (1) variations in subjects’ level of dependence; (2) time following last dose of morphine (4 h in the present study) or illicit opiate (at least 16 h in the other study); (3) statistical methods used; and (4) other factors. Given the many differences between the studies, a direct comparison between the two is not appropriate. However, given that peak, opioid-agonist effects were noted by Mendelson and colleagues to occur within 30 min of intravenous buprenorphine administration, it is likely that the 1-h, post-buprenorphine administration observation period of the present study was sufficient to detect potential drug-related effects.

In another study (Schuh et al., 1996), buprenorphine (6 mg administered intramuscularly) produced significant agonist effects in individuals maintained at 15 or 30 mg of intramuscular morphine daily; effects that were greatly diminished when the same individuals were maintained at 60 or 120 mg of morphine per day. As the present investigation utilized a positive control treatment (morphine) which was associated with significant effects, the lack of an observed effect from buprenorphine is not due to a lack of sensitivity of the measurement instruments.

The results from the present study indicated that the combination of buprenorphine with naloxone in a 4:1 ratio produced significant opioid antagonist-like effects, although not as strong as those produced by naloxone alone. It thus appears likely that the combination of buprenorphine and naloxone used in the present study would have a low potential for intravenous abuse by opioid-dependent individuals. These data are in agreement with a preliminary report (Jones and Mendelson, 1996) that indicated buprenorphine (2 mg) and naloxone combinations in ratios of 2:1, 4:1, and 8:1 were associated with opioid antagonist effects. Although that investigation did not include a naloxone-only treatment...
group, it was reported that the three buprenorphine/naloxone dosage ratios did produce dose-dependent effects. Data from the present study also indicated that the combination of buprenorphine with naloxone may diminish the withdrawal effects induced by naloxone alone. Similar findings were observed in a study (Preston et al., 1988) that utilized methadone-maintained individuals, lower doses of buprenorphine and naloxone, and a higher ratio of naloxone to buprenorphine. Even considering the design and procedural differences between the studies, the results from both indicated that adequately high doses of buprenorphine (relative to naloxone) could potentially blunt the antagonist effects of naloxone. This observation is tempered, however, by the finding that buprenorphine itself may precipitate opioid withdrawal signs and symptoms in methadone-maintained individuals. This effect, though, is apparently modulated by a number of factors, including buprenorphine dose, methadone maintenance dosage, and time of buprenorphine administration relative to the last methadone dose (Strain et al., 1992; Walsh et al., 1995; Strain et al., 1995). In contrast to the precipitation of opioid withdrawal effects by buprenorphine in individuals receiving methadone, buprenorphine (6 mg administered intramuscularly) failed to precipitate significant withdrawal in opioid-dependent subjects receiving 120 mg of morphine parenterally per day (Schuh et al., 1996). It is not clear from data presently available which doses of buprenorphine, dose ratios of buprenorphine to naloxone, or conditions may be necessary for buprenorphine to significantly attenuate the antagonist effects of naloxone in opioid-dependent individuals.

The opioid antagonist effects observed in the present study were more consistent (with regards to statistical significance) on a scale assessing multiple dimensions of withdrawal signs and symptoms than on a visual analog scale considering only ‘bad’ effects. That one scale could be more sensitive than the other was not unexpected, and was the reason that both were included in the present investigation. Results from previous studies (Strain et al., 1992; Walsh et al., 1995; Mendelson et al., 1996) of buprenorphine and/or naloxone in heroin-dependent or methadone-maintained volunteers likewise showed differential sensitivity between visual analog and other rating scales. As can be seen from Fig. 1 and Fig. 2 (bottom panel) of the present study, however, the relative magnitudes of the responses on the different scales were similar.

The results from this study indicated that the combination of buprenorphine with naloxone in a 4:1 ratio produced opioid antagonist-like effects which should limit its potential for intravenous abuse by opioid addicts.

While this is an important consideration, a formulation which combines buprenorphine and naloxone must be effective, safe, and also acceptable to the target treatment population. A sublingual combination product utilizing a 4:1 buprenorphine to naloxone ratio is currently being evaluated in a multisite, efficacy/safety study. If both efficacy and safety are confirmed, this formulation can provide both clinicians and patients with a treatment alternative to methadone and methadyl acetate.

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References


