Buprenorphine alone and in combination with naloxone in non-dependent humans

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This study evaluated the effects of concurrent naloxone on the opioid agonist effects of buprenorphine, a mixed agonist-antagonist marketed as an analgesic and under development as a treatment for drug abuse. In a residential laboratory seven non-physically-dependent opioid abuser volunteers received intramuscular buprenorphine (0.4 mg or 0.8 mg/70 kg) alone and in combination with naloxone (0.4 mg or 0.8 mg/70 kg) versus placebo. Buprenorphine produced dose-related opioid agonist effects on physiological and subjective measures. Concurrent naloxone attenuated the opioid agonist effects of buprenorphine. Thus, a combination product of buprenorphine and naloxone may have lower abuse liability than buprenorphine alone.

Key words: buprenorphine; naloxone; opioid; abuse liability; human

Introduction

Buprenorphine is a semi-synthetic opioid analgesic that has partial agonist activity (Jaffe and Martin, 1990). Several features of buprenorphine make it of special interest. It is an analgesic of potentially lower liability for abuse/dependence (Lewis, 1985) and it is a potential pharmacotherapy for opioid abuse/dependence (Jasinski et al., 1978; Lange et al., 1990). Buprenorphine has high affinity for opioid receptors and a long duration of action that seems more a function of its slow dissociation speed from its receptor than from its long plasma half-life (Hambrook and Rance, 1976).

In addition to its use as an analgesic in acute and chronic pain and in some anaesthetic procedures, buprenorphine has been used in clinical trials for detoxification treatment of opioid addiction (Bickel et al., 1988a; Kosten and Kleber, 1988). Buprenorphine is as efficacious as methadone in the detoxification treatment of narcotic abusers (Bickel et al., 1988a) and it reduces the self-administration of heroin by human subjects in a laboratory analog of treatment (Mello and Mendelson, 1980; Mello et al., 1982). At high doses buprenorphine is able to block the effects of an injected opioid agonist (Bickel et al., 1988b; Jasinski et al., 1978) and, when it is discontinued, only a minimal withdrawal syndrome has been observed (Jasinski et al., 1978; Mello and Mendelson, 1980).

Buprenorphine has been suggested to have lower-addictive liability than other opioid drugs, in part because its ability to induce physical dependency is minimal (Cowan et al. 1977). However, cases of buprenorphine abuse have been published in countries where the drug was widely marketed (Lewis, 1985). In some cases buprenorphine was abused as a heroin substitute (Strang, 1985); in others primary addiction to
buprenorphine was described (Vargas-Castrillon et al. 1987). The addicts directly used the parenteral form and/or prepared the sublingual tablets for injection (Strang, 1985).

The addition of an opioid antagonist has been used as a deterrent to parenteral abuse of opioid analgesics. For example, the addition of naloxone to pentazocine tablets reduced the incidence of pentazocine abuse (Senay and Clara, 1985). Other combinations of opioid agonists and antagonists that have been studied are: methadone-naloxone (Parwatikar and Knowles, 1973; Nutt and Jasinski, 1974) and morphine-nalorphine (Fraser et al. 1956).

The present study is a follow-up to our previous study of the effects of buprenorphine/naloxone combinations in opioid dependent volunteers (Preston et al., 1988). In that study buprenorphine/naloxone combinations precipitated a withdrawal syndrome and showed little if any evidence of abuse liability in opioid-dependent subjects. The present study examined the effects of simultaneous administration of buprenorphine and naloxone in non-physically-dependent subjects. The clinical pharmacological methods used were those generally recognized as providing a valuable index of the likely abuse potential of the test compounds (Jasinski, 1977). The acute profile and time course of effects on subjective, physiologic and behavioral indices of buprenorphine alone and in combination with naloxone were assessed in healthy volunteers with histories of opioid drug abuse.

Methods

Subjects

The participants were seven healthy adult male volunteers with histories of parenteral opioid abuse, but who were not currently physically dependent as determined by history, examination and observation in the laboratory prior to the study's start. Participants were recruited by newspaper advertisements and word-of-mouth referrals, were screened to rule out major psychiatric illness and received a medical evaluation including an ECG prior to their participation.

Mean age was 34.9 years (range, 28–46 years old) and mean weight was 72.1 kg (range, 59.9–84.1 kg). For approximately 3 weeks the subjects resided in a behavioral pharmacology research laboratory which has been previously described (Griffiths et al., 1980). They received a caffeine-free diet and, on a random schedule, urinalysis and breath alcohol testing were conducted to insure abstinence from drugs and alcohol. Subjects participated successively, not simultaneously, in order to increase the independence of observations.

The study was approved by the Institutional Review Board for human research; volunteers provided written informed consent and were paid for their participation. Volunteers were informed that the purpose of the study was to determine the effects of combining buprenorphine and naloxone in people who were not physically dependent on opioids. Possible effects of buprenorphine and naloxone were explained before the subjects participated in the study.

Drugs

Each subject was exposed to the following 7 drug conditions (per 70 kg): (1) placebo, (2) buprenorphine 0.4 mg, (3) buprenorphine 0.4 mg plus naloxone 0.4 mg, (4) buprenorphine 0.4 mg plus naloxone 0.8 mg, (5) buprenorphine 0.8 mg, (6) buprenorphine 0.8 mg plus naloxone 0.4 mg and (7) buprenorphine 0.8 mg plus naloxone 0.8 mg. All drugs were administered by the intramuscular route in 1-ml volumes under double-blind conditions. Drugs were injected into the deltoid muscle of the arm not used for monitoring blood pressure.

Buprenorphine HCL was supplied by Reckitt and Colman Pharmaceutical Division (Hull, England). Buprenorphine was weighed as the salt and dissolved in distilled pyrogen-free water in concentrations equivalent to 0.8 mg/70 kg per 0.5 ml and buffered to pH 4.2. Naloxone solutions were prepared from ampules containing 10 mg/ml naloxone HCl which were supplied by DuPont Pharmaceuticals (Wilmington, Delaware 19898). All dilutions were made with sterile
water for injection under a laminar flow hood using aseptic techniques. Buprenorphine (0.5 ml) and naloxone (0.5 ml) solutions were mixed in a 3 cm³ syringe just prior to administration.

General procedures
The order of the seven drug conditions was randomized, such that each subject was exposed to a unique order of drug conditions with the sequence of conditions counter-balanced across subjects. One drug condition was administered per session and sessions were separated by at least 48 h. Sessions were conducted in a quiet testing room with the subject seated in front of a computer screen and accompanied by a staff observer. No smoking, eating or drinking was permitted during sessions. During each session, subjective, observer-rated, physiological and behavioral effects were monitored periodically before and for 2 h after the drug was administered.

Experimental sessions
Experimental sessions were held in a laboratory adjacent to the residential research unit. Each subject participated in eight sessions. The first session was with placebo and served as practice/training; these data were excluded from analysis. The seven experimental drug conditions (including placebo) were presented in the remaining sessions. All subjective and observer-rated effects were assessed before drug and 15, 30, 45, 60, 90 and 120 min after drug, with the exception of the ARCI, all subjective effects batteries were presented to the subjects on an Apple IIe computer screen. Subjects responded to the computer tasks by using the standard keyboard of the Apple IIe computer or the joy stick controller. Data were recorded, scored and stored by the computer. The ARCI was completed on optically scannable sheets.

Drug class identification questionnaire
The drug class identification questionnaire consisted of a list of ten drug categories, with examples in popular terminology, from which subjects selected the category to which the test drug was most similar. The categories were: placebo, opiate, opiate antagonist, phenothiazine, barbiturate and sleeping medication, antidepressant, hallucinogen, benzodiazepine, stimulant and other.

Visual analog scales
Each visual analog item was rated by positioning an arrow at some point along a 100-point scale from 'none' to 'extremely'. The test drugs were rated for: high, any drug effects, good effects, bad effects, liking and sick.

Adjective rating items
The battery consisted of 15 items. Each item was rated as: 'not at all', 'a little', 'moderately', 'quite a bit', or 'extremely'. The ratings yielded item scores from 0 to 4, respectively. Subsets of the 15 items were used to calculate the opiate agonist and Fraser scales.

Subjective effects measures
A variety of self-report instruments used in our related prior study with dependent subjects (Preston et al., 1988) were used as indices of drug-related subjective effects. With exception of the ARCI, all subjective effects batteries were presented to the subjects on an Apple IIe computer screen. Subjects responded to the computer tasks by using the standard keyboard of the Apple IIe computer or the joy stick controller. Data were recorded, scored and stored by the computer. The ARCI was completed on optically scannable sheets.

Opiate agonist scale. Scores from all 15 items were entered into the calculation of the opiate agonist scale. The 15 items were: turning of stomach, nodding, skin itchy, heavy or sluggish feeling, relaxed, dry mouth, carefree, talkative, good mood, pleasant sick, energetic, drive, drunken, nervous, friendly. The scores on all 15 items were summed to produce the total scale score (range: 0 - 60).
Fraser scale. Scores from ten of the 15 items were entered into the calculation of the Fraser scale. Fraser et al. (1961) had previously shown that these items were sensitive to opiate agonist effects. Items rated as zero received a zero in scoring; items rated as 1 - 4 (i.e. present to some degree) received a score of one or two. The ten items, with their respective scores are: turning of stomach (1), skin itchy (2), relaxed (1), coating (2), talkative (1), pleasant sick (1), drive (2), sleepy (2), drunken (1), nervous (2). The scores on all 10 items were summed to produce the total scale score (range: 0 - 15).

ARCI
The ARCI consists of short statements which require true/false responses. The statements are about subjective feelings and are scored to yield scales that have been empirically validated as sensitive to various types of drug effects (Hill et al., 1963). Subjects completed the 49-item short form version of the ARCI described by Martin et al. (1971). Scores for five scales were calculated: phenobarbital-chlorpromazine-alcohol group (PCAG) scale, commonly used as an index of sedation; the morphine benzedrine group (MBG) scale, commonly used as an index of euphoria; the lysergic acid diethylamide (LSD) scale, commonly used as an index of dysphoria; and the benzedrine group (BG) and amphetamine (A) scales, commonly used as indices of amphetamine-like CNS stimulant effects.

Observer ratings
Observer ratings of subjects' drug effects were made by the research technician monitoring the sessions. Pencil-and-paper forms of the 15 adjective rating items were completed. When evaluating subjects, the observers were blind to the participants' responses. Scale scores were calculated for observers' ratings exactly as for subjects' ratings.

Physiological measures
Pupillary diameter measures were obtained from photographs taken with a modified Polaroid close-up camera in ambient normal room lighting without windows. Photographs were of the right eye and magnified 3 times. Pupil diameters were measured by calipers; vertical and horizontal diameters were averaged and adjusted for magnification.

During sessions (from before drug until 2 h after drug), automated recordings of pulse, blood pressure, respiration rate and skin temperature were obtained. A blood pressure cuff inflated automatically once per min to measure blood pressure and pulse rate (Sentron Automatic Blood Pressure Monitor, Bard Biomedical Div., Lombard, IL). A bellows respiratory band (Pneumo Chest Assembly, Lafayette, IN) was worn around the lower chest and connected to a pressure-sensitive switch (Micro Pneumatic Logic Inc., Fort Lauderdale, FL) to continuously monitor respiration rate. Skin temperature was monitored by a skin thermistor (Yellow Springs Instrument Co., Yellow Springs, OH) taped to the middle finger. An Apple IIe computer (Cupertino, CA) controlled the collection and storage of the physiological data.

Psychomotor/cognitive measures
Two measures of psychomotor/cognitive performance were obtained: a digit symbol substitution task (DSST) and a digit recall task. The computerized version of the DSST has been described by McLeod et al. (1982). The task was 90 s in duration and performance was measured by: number attempted, number correct and percent correct. In the digit recall task, subjects observed an eight-digit number on the computer screen for 3 s. The subjects' task was to replicate the number sequence after the display disappeared from the screen. Five sets of 8-digit numbers were presented at each test interval, and performance was measured by: number of digit position errors (maximum = 40) and number of correct eight-digit numbers.

Post-session measures
After the sessions, pupil diameter measures and all subjective effect measures were collected at 3, 4, 5, 7, 9 and 24 h after drug. These were collected on the residential unit; subjective measures were in pencil and paper format and physiological measures were collected manually.
Data analysis

The drug class identification questionnaire was analyzed by two-factor repeated measures analysis of variance with dose and time as factors. All other variables were analyzed by analysis of covariance, using the pre-drug value as the covariate and dose and time as factors. Probability levels of the factors in the ANCOVAs and ANOVA served to characterize the effects of buprenorphine and naloxone. Because of the short duration of naloxone's effects only within-session measures were included in the statistical analyses. Effects were considered significant if \( P < 0.05 \).

Initially an overall analysis was conducted that included all seven experimental conditions and Tukey post-hoc comparisons to placebo were conducted. Since the primary experimental question was whether naloxone altered buprenorphine's effects, three separate analyses were then conducted: one to assess buprenorphine dose effects, one to assess naloxone dose effects at the lower buprenorphine dose and one to assess naloxone dose effects at the higher buprenorphine dose. Buprenorphine dose effects were determined by analyzing the following conditions: placebo, buprenorphine 0.4 mg and buprenorphine 0.8 mg. Naloxone dose effects in the presence of the lower buprenorphine dose were determined by analyzing the following conditions: buprenorphine 0.4 mg, buprenorphine 0.4 mg plus naloxone 0.4 mg, and buprenorphine 0.4 mg plus naloxone 0.8 mg. Naloxone dose effects in the presence of the higher buprenorphine dose were determined by analyzing the following conditions: buprenorphine 0.8 mg, buprenorphine 0.8 mg plus naloxone 0.4 mg and buprenorphine 0.8 mg plus naloxone 0.8 mg.

Results

Results from the data analyses for drug condition effects are summarized in Table I. The table shows all \( P \)-values less than 0.10. The first column presents the results of the combined analysis of all seven drug conditions; the other columns present the results for the more focused experimental questions. There were significant time effects for most variables for which there were significant drug condition effects; these \( P \)-values are not shown. The time course results for selected measures are presented graphically in Fig. 1 (drug class identification questionnaire), Fig. 2 (subjective indices — visual analog scale Liking and High scores and subject-rated agonist scale scores) and Fig. 3 (objective indices — pupillary diameter, respiratory rate and observer-rated agonist scale scores).

Buprenorphine dose effects

Buprenorphine produced a characteristic opioid-agonist-like profile of effects on both objective and subjective indices (Table I, column 2). Examples of the time course of buprenorphine's effects on both subjective and objective indices are presented in the left-hand panels of Figs. 1–3. Peak effects tended to occur from one to two hours after drug for most variables; however some peak effects (e.g. Liking, identification as an opiate) occurred within 0.5 h. Visual inspection of the post-session data revealed that most effects of buprenorphine had dissipated and returned to normal values by 3–7 h after drug, except pupillary constriction, which remained until sometime between the 9-h and 24-h post-drug assessments.

The most sensitive subjective measure of buprenorphine effects was the drug class identification questionnaire, where highly significant dose-related effects \( (P < 0.001) \) were seen on percent of subjective identifications as an opiate. As shown in the left-hand panel of Fig. 1, the higher dose of buprenorphine was identified as an opiate on 100% of occasions at 30 and 45 min after drug.

Selected subjective effect measures are shown in the left-hand column of Fig. 2. Many subjective effect measures were sensitive to buprenorphine. Visual analog Liking and High showed significant dose-related increases and Good Effects showed a substantial (> 35 points) and near-significant increase. Significant dose-related increases were also observed in the subject-rated agonist scale and subject-rated
Table I. Summary of statistical results. Entries are $P$-values.

<table>
<thead>
<tr>
<th>Drug class identification</th>
<th>Overall analysis</th>
<th>Separate dose effect analyses</th>
<th>Buprenorphine dose effect</th>
<th>Naloxone dose effect</th>
<th>Naloxone dose effect</th>
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<td>Recall correct</td>
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$- P > 0.10; * P < 0.05; ** P < 0.01.$

Fraser scale. On the ARCI, the PCAG (sedation) scale was significantly increased and the BG (stimulation) scale was significantly decreased. Both the MBG (euphoria) scale and the LSD (dysphoria) scale were slightly increased, though not significantly. The A scale was not significantly affected.

Selected physiological and observer-rated
Fig. 1. Acute effects of buprenorphine and naloxone on drug class identification. Values are means.

Fig. 2. Acute effects of buprenorphine and naloxone on subjective measures of drug effects. Values are adjusted means from the analyses of covariance.
effects are shown in the left-hand column of Fig. 3. As is typical of opioid agonists, buprenorphine produced significant dose-related constriction of pupillary diameter and depression of respiratory rate. Near significant increases on the observer-rated agonist scale were also obtained. Diastolic blood pressure increased near-significantly by an average of 4–5 mmHg after the higher dose of buprenorphine.

Buprenorphine produced a significant though small dose-related performance decrement in the number of correct responses on the DSST task. Although both the number of problems attempted and the percent correct were also slightly reduced with increasing doses of buprenorphine, the changes were not significant.

Naloxone dose effects

When given concurrently with buprenorphine, naloxone reduced the effects of both the lower dose of buprenorphine (Table I, column 3) and the higher dose of buprenorphine (Table I,
column 4). Examples of the time course of naloxone's dose-related effects on subjective and objective indices are presented in the center and right-hand panels of Figs. 1–3. The effects of naloxone on the lower dose of buprenorphine are shown in center panels and the effects of naloxone on the higher dose of buprenorphine are shown in right-hand panels. While there was some variability across different measures, naloxone's peak effects occurred during the first hour after drug.

The most sensitive subjective index of naloxone's effects was the drug class identification questionnaire. With the lower dose of buprenorphine, naloxone produced near-significant reductions in the percent of opiate identifications. Buprenorphine 0.4 mg with naloxone 0.8 mg was never identified as an opiate (Fig. 1, center panel). With the higher dose of buprenorphine, naloxone significantly reduced the percentage of opiate identifications on the drug class identification questionnaire (Fig. 1, right-hand panel).

Additional selected subjective effect measures of naloxone are shown in the center and right columns of Fig. 2. With the lower dose of buprenorphine, naloxone produced near-significant reductions in the percent of opiate identifications. Buprenorphine 0.4 mg with naloxone 0.8 mg was never identified as an opiate (Fig. 1, center panel). With the higher dose of buprenorphine, naloxone significantly reduced the percentage of opiate identifications on the drug class identification questionnaire (Fig. 1, right-hand panel).

Selected observer-rated and physiological effects are shown in the center and right columns of Fig. 3. With the lower dose of buprenorphine, naloxone significantly reduced the increases on the observer-rated opiate agonist scale. With the lower dose of buprenorphine, naloxone produced near-significant reductions in heart rate (average of 3–4 beats/min). With the higher dose of buprenorphine, naloxone significantly attenuated the constriction of pupillary diameter and depression of respiratory rate. Naloxone had no effect on performance of psychomotor tasks.

The Tukey post-hoc comparisons from the overall seven-condition analyses were too extensive to report in detail, but the pattern of results was confirmatory of naloxone's attenuating the effects of buprenorphine. For those variables and time points for which buprenorphine alone produced significant differences from placebo, combinations of buprenorphine and naloxone tended to produce nonsignificant differences during the earlier portions of the time course (i.e., the first hour). Thus, the effect of naloxone was primarily to delay the onset of buprenorphine effects; however, the buprenorphine-naloxone combinations often produced significant differences from placebo later in the session despite this early attenuation. This presumably reflects naloxone's relatively short duration of action. The limited duration of naloxone's activity can be seen in Fig. 2 for subject-rated Liking and High and in Fig. 3 for pupillary diameter.

**Discussion**

In general, the current findings concerning the effects of buprenorphine alone are similar to those previously reported by Jasinski et al. (1978). They reported that following single subcutaneous doses of buprenorphine 0.2–2.0 mg, non-dependent subjects showed a typical opioid-agonist-like profile of effects — i.e. dose-related increases in pupillary constriction, ratings of subjective liking, identifications as an opiate, increases in the MBG and PCAG scales of the ARCI and in opiate agonist signs and symptoms.

The primary purpose of the present study was to assess whether concurrent administration of the opioid antagonist naloxone would alter (attenuate) the agonist effects of buprenorphine. The results indicate that such attenuation does occur. Concurrent naloxone exerted sufficient antagonist effects to significantly reduce both the subjective and the physiological effects of buprenorphine. The fact that this attenuation was not uniform across all assessment indices may be due to differing magnitudes of buprenorphine effects and differing error variances across different indices. For example, buprenorphine 0.4 mg/70 kg produced such modest effects that even the total elimination by
naloxone of all agonist effects on some indices was sometimes not statistically significant (e.g. the effect of buprenorphine 0.4 mg/70 kg plus naloxone 0.8 mg/70 kg on subjective identification as an opiate (Fig. 1) and on various other subjective indices (Fig. 2)).

The attenuation of buprenorphine's effects by concurrently administered naloxone may depend less upon the absolute amount of naloxone administered and more upon the ratio of naloxone to buprenorphine. With buprenorphine 0.4 mg/70 kg the naloxone/buprenorphine ratios studied were 1:1 and 2:1; with buprenorphine 0.8 mg/70 kg the naloxone/buprenorphine ratios studied were 1:2 and 1:1. The present data indicate that for most measures, the opioid agonist effects of buprenorphine were reduced to placebo levels when the dose ratios of naloxone/buprenorphine were 2:1. Further studies of higher naloxone/buprenorphine ratios (e.g. 2:1, 4:1) would certainly be informative, especially with buprenorphine doses that produce substantial effects alone (i.e. 0.8 mg and higher). Animal laboratory data using a drug avoidance procedure (or a passive self-administration procedure) also indicate that a naloxone/buprenorphine ratio of 2:1 or greater may be necessary to attenuate the reinforcing effects of buprenorphine (Hoffmeister, 1986).

The present data indicating that concurrent naloxone can attenuate the opioid agonist effects of buprenorphine suggest that a combination product of buprenorphine plus naloxone may have lower abuse potential than buprenorphine alone. The present findings in this regard are complementary to an earlier study with opioid dependent volunteers which reached a similar conclusion (Preston et al., 1988). In that study methadone-dependent volunteers received buprenorphine (0.2 and 0.3 mg) in combination with naloxone 0.2 mg (approximately a 1:1 ratio) subcutaneously, which precipitated an opioid withdrawal reaction comparable to that precipitated by 0.2 mg naloxone alone. Other studies, in non-dependent patients with post-operative pain, have shown that similar buprenorphine/naloxone combinations, when administered intramuscularly, retain analgesic efficacy comparable to that of buprenorphine alone (Rolly et al., 1986; Vanacker et al., 1986).

Concern about the abuse liability of buprenorphine and interest in a possible buprenorphine/naloxone combination product arise from two sources. One is the possibility of illicit diversion and abuse of buprenorphine products marketed for analgesia. The second is the fact that buprenorphine is being evaluated as a potential treatment medication for drug abuse and drug abuse patients could be expected at least to attempt abuse of any such medication. Buprenorphine is marketed as an analgesic in both parenteral and sublingual formulations, though only the parenteral formulation is currently available in the USA. Sublingual formulations are being evaluated for efficacy as a drug abuse treatment medication. The route of administration is likely to affect abuse liability and is likely to influence the efficacy of naloxone combinations in attenuating abuse liability. Illicit opioid abuse typically occurs parenterally. The sublingual versus parenteral activities of naloxone and buprenorphine differ such that naloxone is proportionately more active via the parenteral route than is buprenorphine. Previous work has concluded naloxone's sublingual activity to be only 5-10% of its parenteral activity (Preston et al., 1990), whereas buprenorphine's sublingual activity is about 67% of its parenteral activity (Jasinski et al., 1989). Thus, it should be possible to produce a sublingual buprenorphine/naloxone combination product that would have little naloxone bioavailability when properly used via the sublingual route, but which would deliver substantial naloxone if diverted and misused via the parenteral route. The present data indicate that such concurrent parenteral delivery is likely to have lower abuse liability than that of buprenorphine alone.

Overall, we conclude that combinations of buprenorphine and naloxone show promise as a strategy for further reducing the abuse potential of buprenorphine. This will be most true in the case of opioid dependent subjects, where a withdrawal reaction is precipitated. This strategy is also most likely to be effective in reducing abuse by the parenteral route, since it
is unclear whether sufficient amounts of naloxone would be delivered by other routes. Further studies of higher buprenorphine doses, of higher naloxone/buprenorphine ratios and of other routes of administration would be useful.

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References


