Buprenorphine and Naloxone Interactions in Methadone Maintenance Patients

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Buprenorphine is undergoing clinical trials for the treatment of opiate addiction. Although the abuse liability of sublingual buprenorphine is low, reports of intravenous abuse have appeared. This study describes the physiologic and subjective effects of intravenously administered buprenorphine and naloxone given alone and in combination to methadone-maintained patients (40–60 mg/day). On four separate occasions at least 1 day apart, 6 subjects were administered either 0.2 mg buprenorphine, 0.1 mg naloxone, 0.2 mg buprenorphine and 0.1 mg naloxone in combination, or placebo. One male subject quit the experiment after three sessions because of excessive opiate withdrawal. Buprenorphine produced no significant physiologic or subjective effects. Naloxone produced marked opiate withdrawal symptoms. Buprenorphine in combination with naloxone produced characteristic physiologic and subjective opiate antagonist-like symptoms and signs. The parenteral abuse potential of the buprenorphine and naloxone combination is discussed. © *1997 Society of Biological Psychiatry*

Key Words: Buprenorphine, naloxone, methadone, opiate antagonist, intravenous administration, opiate withdrawal

BIOL PSYCHIATRY 1997;41:1095–1101

Introduction

Buprenorphine hydrochloride is a partial opiate agonist being evaluated for the treatment of opiate addiction (Kosten et al 1991; Johnson et al 1992; Strain et al 1994; Ling et al 1994). Buprenorphine has numerous advantages in the treatment of opiate addiction over previously used pharmacotherapies. It can be administered sublingually (Jasinski et al 1989) and is effective in suppressing heroin self-administration in humans (Mello and Mendelson 1980). Abrupt cessation of buprenorphine use generally produces only a mild to moderate abstinence syndrome (Jasinski et al 1978; Fudala et al 1990; Kosten et al 1991). The abuse liability of sublingual buprenorphine appears to be low (Lewis 1985); however, reports of intravenous buprenorphine abuse among opiate-dependent individuals have appeared (Strang 1985; Robertson et al 1986; Robinson et al 1993; Nigam et al 1994). Within any population

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Received October 13, 1995; revised April 29, 1996.

0006-3223/97/$17.00
PII S0006-3223(96)00266-1

Table 1. Subject Demographics

Age	Sex	Race	Current methadone dose	Length of time at this dose	Length of time in current program	Previous methadone treatment
50[a]	M	B	50 mg	1 year	2 years	None
39	M	W	45 mg	1 year, 6 months	2 years	None
43	M	W	45 mg	2 years	2 years	1989
37	F	W	45 mg	1 month	1.5 years	1980, 1982
47	M	H	60 mg	3 months	3 years	None
33	M	H	50 mg	2 years, 5 months	20 months	None

B, black; W, white/Caucasian; H, Hispanic.
[a] Subject was excluded from the statistical analysis.

of drug users, various routes of illicit drug administration may be used. Therefore, the abuse liability of buprenorphine may differ between sublingual and intravenous routes. Additionally, individuals already heavily dependent on opiates, such as those on methadone maintenance, may be more likely to abuse drugs intravenously than casual or nondependent users.

One mechanism to diminish parenteral abuse and illicit diversion of buprenorphine might be a combination of buprenorphine with naloxone. The purpose of combining naloxone with an opiate analgesic is to decrease parenteral abuse potential by increasing or actively precipitating opiate withdrawal in physically dependent abusers. The relatively low oral and sublingual bioavailability (Weinhold et al 1992) and rapid and intense effects of naloxone (Gilman et al 1990) when given intravenously makes it an ideal candidate for a combination formulation. Opiate analgesics such as morphine (Gupta and Dundee 1974), methadone (Nutt and Jasinski 1974; Parwatikar and Knowles 1973), and pentazocine (Ghodse 1987) have been combined with naloxone in various doses and ratios. These combinations have resulted in diminished abuse liability, particularly for pentazocine. Buprenorphine and naloxone combinations are likely to produce a similar decrease in abuse liability with the greatest effects in populations of strongly opiate-dependent intravenous users (i.e., methadone maintenance patients or untreated addicts).

This study describes the results of a placebo-controlled, double-blind study measuring the effects of intravenous buprenorphine, buprenorphine and naloxone in combination, and naloxone alone in methadone-maintained patients on doses between 40 and 60 mg per day. Buprenorphine and naloxone were tested in dose ratios similar to a previously studied subcutaneous combination (Preston et al 1988). In contrast to prior studies, we administered doses intravenously. A modest dose of buprenorphine and naloxone in a 2:1 dose ratio was administered and the effects of buprenorphine and the buprenorphine and naloxone combination were contrasted with either buprenorphine or naloxone alone.

Methods

Subjects

Six subjects were recruited but only 5 completed all study procedures. Due to extreme precipitated withdrawal symptoms, 1 subject refused to complete the final session.

Subjects who completed the study were 4 men and 1 woman, 33–47 years of age (mean, 39.8 ± 5.4 years). Demographic data are in Table 1.

Subjects were recruited through the San Francisco General Hospital Drug Abuse Services Methadone Maintenance Treatment program. Written informed consent was obtained and subjects were paid for their participation. The study was approved by the Committee on Human Research, University of California, San Francisco.

Prior to enrollment, subjects were given a complete medical examination and laboratory screening tests to determine their general physical health. Women were required to test negative for pregnancy, and the adequacy of their current birth control methods was evaluated. To participate, subjects were from 21 to 50 years of age, on a stable dose of 40 mg to 60 mg per day of oral methadone for at least 3 months, and not dependent on alcohol or other illicit drugs according to DSM-III-R criteria (American Psychiatric Association 1987).

Subjects arrived at the laboratory at 8 AM and were tested as outpatients. They were told to abstain from psychoactive drugs (including nicotine and caffeine, but excluding the previous day's methadone dose) for 24 hours before each session. Prior to the testing session, urine samples were collected and screened for the presence of illicit drugs. Cigarette smoking was allowed 1 hour after drug administration. A light lunch was provided 3 hours after dosing. Subjects were escorted back to the clinic for their daily methadone dose where heart rate, blood pressure, and subjective intoxication rating were monitored for 2 hours following methadone dosing.

Drug Dose

Each subject was tested on four occasions with at least 1 day between testing sessions. Intravenous drug conditions were as follows: buprenorphine, 0.2 mg; naloxone, 0.1 mg; buprenorphine, 0.2 mg and naloxone, 0.1 mg; placebo. The sequence of conditions was balanced across sessions in a 4 × 4 Latin square design. Subjects and observers were unaware of the treatment sequence.

Commercially available, pharmaceutical grade supplies of buprenorphine (Buprenex) and naloxone (Narcan) were used. Dose combinations were made up in fixed volumes of saline. After a 30-min period of recording to establish baseline cardiovascular indices, subjects were given a single intravenous dose of the buprenorphine and naloxone combination (1 mL volume) injected into a rapidly flowing intravenous saline drip over a 30-sec interval. Saline (0.9%) was used for the placebo condition.

Experimental Procedure

MEASURES. Physiologic measures were collected using a vital signs monitor (Model VSM 2, Physio-Control Corp., Redmond, WA). A thermistor taped to the left index finger was used to measure skin temperature. Systolic and diastolic blood pressure, heart rate, and skin temperature were measured at baseline (30, 15, and 5 min prior to drug dose) and at 1, 2, 3, 4, 5, 10, 20, 30, 40, 45, 60, 90, 120, and 180 min postdose. Rate pressure product was calculated by multiplying systolic blood pressure times heart rate. Pupil sizes under dim, dark, and bright light conditions were measured with an automated noncontact monitoring system (EM/2 System, OculoKinetics, Inc., Torrance, CA). Measurements were obtained at baseline and at 2, 20, 40, 80, and 140 min after drug injection.

Visual analog scales were used to rate the degree of drug liking on a 0–100 scale. Subjects rated drug effects by moving an arrow along a 10-cm line anchored at opposite ends with 0 (no effects) and 100 (maximal effect) using a handheld computer. Items on the visual analog included: drug liking, "good" drug effect, "bad" drug effect, "high," drunkenness, "sickness," and sleepiness. Visual analog scale ratings were obtained before drug administration and at 5, 15, 30, 45, 60, 90, 120, and 180 min postdose.

The opiate agonist and opiate withdrawal scales each listed 20 adjectives describing typical opiate agonist effects and withdrawal symptoms (Bickel et al 1988). Subjects indicated the degree of opiate-like or abstinence-like effects on a scale of 0–4, with 0 as no effect and 4 as maximum effect (maximum possible total score = 80). Opiate agonist and withdrawal ratings were obtained at the same times as the visual analog scale.

Total abstinence scale scores were also determined by summing selected maximum physiologic changes and the withdrawal rating changes from pre- to postdrug administration (Jones 1981). An increase of 2 beats/min in heart rate, 2 mmHg in blood pressure, and a drop in skin temperature of 0.5°C were scored as one point each. An increase of 0.1 mm in pupil size scored three points. Observation times were the points of maximal change occurring within the first 45 min postdose.

Subjects verbally rated their global estimate of opiate intoxication ("high") and global opiate withdrawal on a scale of 0–100, with 0 as no effect and 100 as the most extreme effect. Global intoxication and withdrawal ratings were obtained at the same time points as heart rate and blood pressure determinations.

Statistical Analysis

Six subjects were enrolled in this study, but only 5 completed all four sessions. The 6th subject missed his placebo session and the last half of the session when he received the combination of buprenorphine and naloxone. The completed (two and one half) sessions for this subject had large amounts of missing data. The data were analyzed for the 5 subjects who completed the study and then reanalyzed with the 6th subject included. Study results were not altered by inclusion of the 6th subject. The reported data for this study represent the 5 subjects who completed all study sessions.

Treatment effects on physiologic and subjective measures were analyzed by repeated-measures analysis of variance (ANOVA). Drug condition and time were considered within-subject factors. After a significant F test, pairwise comparisons were performed using the least squares means analysis. Scores for the total abstinence scale were compared using ANOVA repeated measures with condition as the within-subject variable. Change scores (post- minus pretreatment) were used in the analyses. Effects were considered significant at $p \leq .05$. Session effects were analyzed by ANOVA repeated measures with session order and times as within-subject variables.

Results

Physiologic Measures

Significant differences between conditions were seen in systolic and diastolic blood pressure and rate pressure product. Systolic blood pressure was significantly increased in the buprenorphine and naloxone combination and the naloxone alone conditions when compared with placebo or buprenorphine ($p < .02$). Peak effects occurred within 5 min postinjection and treatment conditions remained significantly different for 40 min postdose. Dia-

Table 2. Peak Effects for Cardiovascular Measures and Opiate Antagonist and Agonist Effects (n = 5)

	Buprenorphine[a]	Buprenorphine/naloxone[b]		Naloxone[c]		Placebo[d]	
	Peak mean ± SD	Peak mean ± SD	p^e value	Peak mean ± SD	p^e value	Peak mean ± SD	p^e value
Cardiovascular measures							
Systolic blood pressure	123 ± 7	134 ± 7	0.04	138 ± 11	0.01	123 ± 13	ns
Diastolic blood pressure	81 ± 7	90 ± 6	0.02	94 ± 9	0.01	80 ± 9	ns
Heart rate	86 ± 18	89 ± 13	ns	91 ± 12	ns	86 ± 16	ns
Rate pressure product	10600 ± 3000	11800 ± 2100	ns	12600 ± 1900	ns	10800 ± 3800	ns
Opiate antagonist measures							
Visual analog—sickness	13 ± 29	49 ± 39	0.01	56 ± 33	0.01	7 ± 15	ns
Visual analog—bad drug	15 ± 30	73 ± 19	0.01	64 ± 15	0.01	6 ± 14	ns
Opiate withdrawal scale	0 ± 0	18 ± 25	ns	14 ± 9	ns	2 ± 4	ns
Global withdrawal	0 ± 0	20 ± 44	ns	16 ± 21	ns	0 ± 0	ns
Opiate agonist measures							
Visual analog—drug liking	11 ± 24	21 ± 21	ns	9 ± 13	ns	12 ± 26	ns
Visual analog—good drug	14 ± 30	25 ± 43	ns	9 ± 13	ns	13 ± 30	ns
Visual analog—high rating	12 ± 25	27 ± 28	ns	18 ± 25	ns	7 ± 16	ns
Visual analog—drunkenness	0 ± 0	21 ± 28	ns	21 ± 25	ns	6 ± 13	ns
Visual analog—sleepiness	16 ± 36	28 ± 17	ns	38 ± 29	ns	12 ± 27	ns
Opiate agonist scale	6 ± 7	13 ± 9	ns	11 ± 9	ns	6 ± 4	ns
Global intoxication	0 ± 0	17 ± 23	ns	32 ± 44	0.04	4 ± 9	ns

[a]Buprenorphine 0.2 mg; naloxone 0 mg.
[b]Buprenorphine 0.2 mg; naloxone 0.1 mg.
[c]Buprenorphine 0 mg; naloxone 0.1 mg.
[d]Buprenorphine 0 mg; naloxone 0 mg.
[e]All comparisons (p values) are to the buprenorphine condition. p values are for the overall pairwise comparisons of time course.

stolic blood pressure increased by a similar magnitude in the two groups receiving naloxone ($p < .01$). Peak effects occurred within 5 min of drug administration and persisted for 20 min postdose.

There were no significant differences in heart rate between conditions. There was, however, a tendency for heart rate to remain higher in the buprenorphine and naloxone combination and, to a lesser extent, in the naloxone condition when compared with placebo and buprenorphine values. As expected from the effects of the combination formulation and naloxone alone on heart rate and systolic blood pressure, rate pressure product was significantly increased in those conditions where naloxone was administered ($p = .05$).

There were no significant differences between any of the treatment conditions in skin temperature ($p = .57$) or pupil size under dim ($p = .70$), dark ($p = .67$), and bright ($p = .84$) light conditions.

Subjective Measures

A statistical summary of results and peak effects for cardiovascular, opiate antagonist, and agonist effects is shown in Table 2. Time course, peak mean, and individual variability for "bad" drug effect and "sickness," and opiate agonist and opiate withdrawal ratings are illustrated in Figure 1.

VISUAL ANALOG SCALE—BAD DRUG EFFECT. There was a significant difference between conditions on this scale ($p < .01$). This rating was significantly higher after administration of the buprenorphine and naloxone combination and naloxone alone compared with the placebo and buprenorphine conditions. Effects peaked within 15 min of drug administration. Conditions remained significantly different at 60 min postdose. Peak mean ± SD was 73 ± 19 for the buprenorphine and naloxone combination and 64 ± 15 for naloxone alone, compared with 15 ± 30 and 6 ± 14 in the buprenorphine and placebo conditions, respectively. No significant differences were found between the buprenorphine and naloxone combination and naloxone alone.

VISUAL ANALOG SCALE—SICKNESS RATING. There was a significant difference between conditions in sickness rating ($p < .05$). Compared with placebo and buprenorphine conditions, sickness rating was significantly increased by administration of the combination formulation and naloxone alone. Peak effects appeared within 15 min postdose. Peak mean ± SD was 54 ± 32 and 49 ± 39 in the naloxone alone and the buprenorphine and naloxone combination, respectively, compared with 13 ± 29 for buprenorphine alone and 7 ± 15 for placebo. No significant differences were found between the buprenorphine and naloxone combination and naloxone.

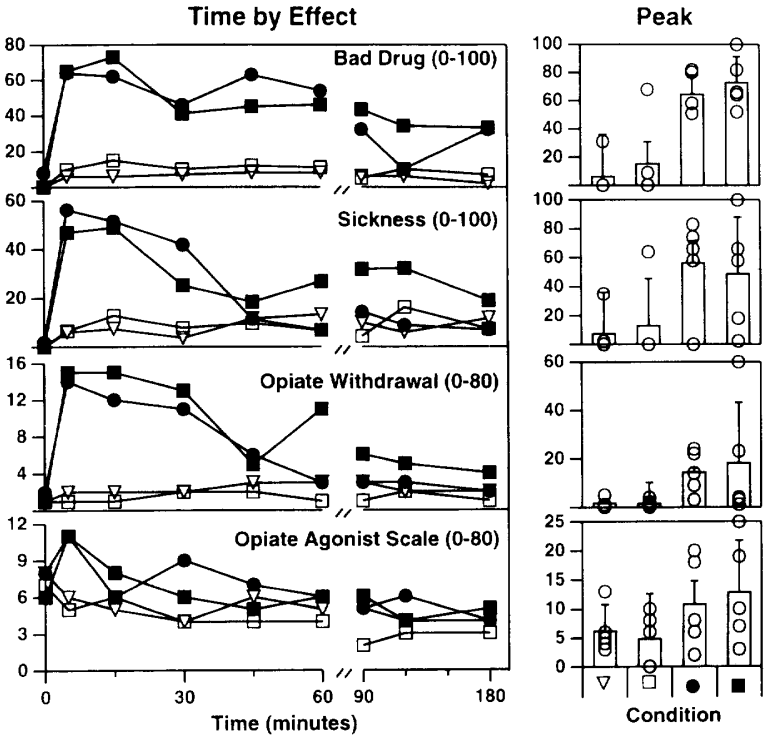

Figure 1. Time course, peak mean, and individual values for intravenous buprenorphine (0.2 mg) (□), naloxone (0.1 mg) (●), buprenorphine (0.2 mg) and naloxone (0.1 mg) (■), and placebo (▽) on the visual analog "bad drug" effect and "sickness" ratings and the opiate withdrawal and opiate agonist scales. Values are means for 5 subjects.

No differences were found in any of the other scales (sleepiness, high, good drug, drunk, drug liking) on the visual analog scale.

TOTAL ABSTINENCE AND OPIATE WITHDRAWAL SCALES. Total abstinence scores were substantially higher after administration of buprenorphine and naloxone in combination and naloxone alone than after buprenorphine alone or placebo. Similarly, rating on the opiate withdrawal scale increased following the buprenorphine and naloxone and naloxone alone conditions; however, the total abstinence score did not achieve significance ($p = .11$), nor did opiate withdrawal rating scores ($p = .10$) when conditions were compared. This is a result of the highly variable data obtained in this small sample.

OPIATE AGONIST SCALE. Opiate agonist rating was not significantly different between any of the drug conditions ($p = .38$).

GLOBAL OPIATE INTOXICATION AND WITHDRAWAL. The global opiate intoxication rating was not significantly different between conditions ($p < .11$). Although global estimates of intoxication increased after administration of the buprenorphine and naloxone combination and naloxone alone, no significant differences were seen. Interestingly, naloxone alone produced a more intense (higher) rating at peak time than the buprenorphine and naloxone combination.

The global opiate withdrawal rating scale showed no significant differences between conditions ($p < .26$). Again, objective global estimates of withdrawal increased after administration of the buprenorphine and naloxone combination and naloxone alone, but the rating was highly variable and did not provide adequate discrimination between drug conditions.

A significant sessions effect was noted for global high rating ($p < .03$) and opiate agonist rating scales ($p < .01$). Global high and opiate agonist effects were significantly higher during the first session of testing when compared with the other three sessions.

Discussion

This study examined the effects of an intravenous buprenorphine and naloxone combination in methadone patients on doses between 40 and 60 mg per day. These individuals represent physically dependent opiate abusers who might have a significant potential for abusing new opiate drugs. Relatively modest doses of buprenorphine

and naloxone were given in dose ratios proposed for use in treatment programs. To facilitate comparisons with previously published data (Preston et al 1988), we selected doses similar to those previously reported. Because most parenteral opiate abusers prefer intravenous (not intramuscular or subcutaneous) administration, we studied the effects of intravenous buprenorphine and buprenorphine and naloxone combinations. Intramuscular buprenorphine is rapidly absorbed, with peak concentrations within 5 min; however, pharmacokinetic differences between intravenous and intramuscular buprenorphine are present for the first 10 min (Bullingham et al 1980). Pharmacodynamic differences between intravenous, intramuscular, and subcutaneous buprenorphine have not been investigated to date. No data are available on subcutaneous buprenorphine pharmacokinetics.

In our subjects, intravenous buprenorphine, 0.2 mg, generally produced opiate agonist effects no different than those seen after placebo. Naloxone, 0.1 mg, produced severe opiate withdrawal signs and symptoms. The combination of buprenorphine and naloxone produced withdrawal as great or greater than naloxone alone and resulted in 1 subject precipitously leaving the study. Although we had intended to study 8 subjects, our clinical impressions and objective findings of severe precipitated withdrawal following combined buprenorphine and naloxone supported early termination of the study.

The combination formulation of buprenorphine and naloxone was qualitatively more like an opiate antagonist than an opiate agonist on all variables examined. Buprenorphine and naloxone combined produced opiate antagonist-like effects on heart rate, systolic, and diastolic blood pressure. Similar subjective effects were seen on opiate withdrawal ratings, total abstinence scores, sickness, and bad drug effect ratings, although great variability was noted between subjects. No subject found the buprenorphine and naloxone combination to be pleasant or to have a significant "good" drug effect. Although some opiate agonist and intoxicating effects were seen in this study, they were generally confined to the first treatment session, perhaps reflecting subject anticipation at receiving a novel or new opiate agonist agent. All subjects found the buprenorphine and naloxone combination and naloxone alone to be significantly dysphoric and unpleasant.

Our findings are in agreement and extend prior evaluations of buprenorphine and naloxone combinations given by other routes to patients with varied opiate use histories. In nonopiate-dependent populations, combined intramuscular doses of buprenorphine and naloxone blunted opiate agonist effects of buprenorphine (Weinhold et al 1992), and in opiate-dependent, methadone-maintained populations, subcutaneous doses of buprenorphine and naloxone precipitated opiate withdrawal (Preston et al 1988). Subcutaneously administered buprenorphine and naloxone combinations in patients maintained on 30 mg of methadone per day produced minimal opiate agonist effects; however, both naloxone at a dose of 0.2 mg and the combination of naloxone (0.2 mg) with buprenorphine (0.3 mg) produced opiate abstinence effects that were quantitatively similar (Preston et al 1988).

In our patients, intense precipitated withdrawal occurred with the intravenous dose combination. Although larger doses of buprenorphine may result in more opiate agonist effects in this opiate-tolerant population, it is not clear if more buprenorphine would blunt the intense precipitated withdrawal induced by naloxone. The 2:1 combination ratio of intravenous buprenorphine (0.2 mg) and naloxone (0.1 mg) appears to have a low abuse liability in methadone-maintained patients. In those individuals with minimal opiate use and no marked tolerance for parenteral opiates, this dose combination may have less predictable effects; however, in one population of individuals likely to abuse opiates intravenously, i.e., those now on methadone maintenance, this combination would appear to severely deter parenteral abuse.

This work was supported by USPHS Contract No. 271-90-7307 and Grants No. DA-01696 and DA-00053 from the National Institute on Drug Abuse, National Institutes of Health.

The authors wish to thank Isabella Fernandez, Tina Melby, and Peter Shwonek for their assistance in conducting this study, Bob Jimison for graphic presentations, and Kaye Welch for editorial assistance.

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