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ORIGINAL INVESTIGATION

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Effects of buprenorphine/naloxone in opioid-dependent humans

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Abstract *Rationale:* Buprenorphine is a partial mu opioid agonist under development as a sublingual (SL) medication for opioid dependence treatment in the United States. Because buprenorphine may be abused, tablets combining buprenorphine with naloxone in a 4:1 ratio have been developed to reduce that risk. Low doses of injected buprenorphine/naloxone have been tested in opioid-dependent subjects, but higher doses (more than 2 mg of either medication) and direct comparisons to SL buprenorphine/naloxone have not been examined. *Objectives:* To assess and compare the effects of intramuscular (IM) versus SL buprenorphine/naloxone in opioid-dependent volunteers. *Methods:* Opioid-dependent volunteers were maintained on 40 mg per day of oral hydromorphone while on a residential research ward. After safety testing in two pilot subjects, participants (n=8) were tested with both IM and SL buprenorphine/naloxone (1/0.25, 2/0.5, 4/1, 8/2, 16/4 mg); IM hydromorphone (10 mg) and naloxone (0.25 mg); both IM and SL buprenorphine alone (8 mg); and placebo. Test sessions were twice per week; dosing was double-blind. *Results:* Intramuscular buprenorphine/naloxone produced dose-related increases on indices of opioid antagonist effects. Effects were consistent with naloxone-precipitated withdrawal, and were short-lived. As withdrawal effects dissipated, euphoric opioid agonist effects from buprenorphine did not appear. Sublingual buprenorphine/naloxone produced neither opioid agonist nor antagonist effects. *Conclusions:* Intramuscular injection of buprenorphine/naloxone precipitates withdrawal in opioid dependent persons; therefore, the combination has a low abuse potential by the injection route in this population. Sublingual buprenorphine/naloxone by tablet is well tolerated in opioid dependent subjects, and shows neither adverse effects (i.e., precipitated withdrawal) nor a high abuse potential (i.e., opioid agonist effects).

Keywords Agonist-antagonist · Buprenorphine · Buprenorphine/naloxone · Hydromorphone · Naloxone · Opioid dependence · Opioid

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Introduction

Buprenorphine is an opioid mixed agonist-antagonist that is effective in the treatment of opioid dependence (Bickel et al. 1988; Johnson et al. 1992, 1995; Kosten et al. 1993; Strain et al. 1994; Ling et al. 1996, 1998; Schottenfeld et al. 1997). The analgesic form of buprenorphine is approved in the United States for use only by injection, but this method of delivery is not optimal when treating opioid dependent outpatients on a daily or near-daily basis. Buprenorphine has relatively poor oral bioavailability; hence, development has focused upon a sublingual delivery system, because good bioavailability is possible by this route. Early clinical studies of buprenorphine used an SL solution, but this form has practical limitations (i.e., preparation, storage and administration, and easier abuse by injection). For these reasons, interest has focused upon the development of a buprenorphine tablet for SL administration. Such a formulation is currently marketed in France, where an estimated 55,000 patients were receiving buprenorphine as of 1998 (Auriacombe 2000).

Buprenorphine is a partial mu agonist and kappa antagonist (Rothman et al. 1995). As with other mu agonist opioids, abuse of buprenorphine is possible, and has been reported from several countries (Strang 1985;

O'Connor et al. 1988; Gray et al. 1989; Singh et al. 1992; Robinson et al. 1993). Since an SL tablet must be water soluble, it is possible that buprenorphine tablets could be dissolved and injected. Acute doses of parenteral buprenorphine produce opioid agonist-like effects in opioid dependent subjects (Schuh et al. 1996; Strain et al. 1997).

Because of this potential for abuse of buprenorphine tablets, interest has shifted to the development of a buprenorphine tablet that also contains naloxone. Unlike buprenorphine, low doses of naloxone have poor SL bioavailability (Preston et al. 1990). Thus, a buprenorphine/naloxone tablet taken by the therapeutic route (i.e., SL) should produce a predominant buprenorphine effect. However, if such a tablet were dissolved and injected by an opioid dependent person, naloxone would produce a precipitated opioid withdrawal syndrome.

In opioid-dependent volunteers parenteral administration of the buprenorphine/naloxone combination precipitates a withdrawal syndrome (Preston et al. 1988; Mendelson et al. 1996, 1997, 1999; Fudala et al. 1998). These studies have generally tested a low range of buprenorphine/naloxone doses; the highest parenteral buprenorphine dose tested has been 2 mg, and the highest parenteral dose of naloxone tested has also been 2 mg (both alone and combined with 2 mg buprenorphine; Mendelson et al. 1996). Based upon human laboratory studies of different dose ratios of buprenorphine to naloxone (e.g., Fudala et al. 1998; Mendelson et al. 1999), the United States National Institute on Drug Abuse (NIDA) has selected buprenorphine/naloxone tablets with a 4:1 dose ratio for clinical testing.

While low doses of combination buprenorphine/naloxone precipitate withdrawal in dependent subjects, combinations incorporating the larger buprenorphine doses typically used in addiction treatment (8 mg and above) have not been previously tested. In addition, previous studies of buprenorphine/naloxone have tested the effects of this combination when given by injection, but not sublingually. Low doses of SL naloxone may not precipitate withdrawal in opioid dependent subjects, but higher doses can. In a study of SL naloxone in opioid dependent volunteers, naloxone doses of 1–2 mg were identified as the approximate threshold above which subjects experienced precipitated withdrawal (Preston et al. 1990). It is possible that some patients might experience precipitated withdrawal from the combination product taken by the SL route because dosing of buprenorphine/naloxone is expected to be at least 8–16 mg per day of buprenorphine combined with 2–4 mg naloxone.

The purpose of this study was to assess the effects of buprenorphine/naloxone combinations over a broad dose range when administered by both the SL and parenteral routes to opioid dependent volunteers. The study sought to determine how buprenorphine and naloxone might influence the effects of each other, as a function of both dose and route of administration. In addition, the study included testing of doses of buprenorphine without naloxone, prototypic opioid agonist and antagonist control conditions, and placebo. The results from this study provide information about how the combination of an opioid agonist with an opioid antagonist produce differential predominating effects when administered by different routes of administration. These results are also relevant to the clinical development and use of buprenorphine and buprenorphine/naloxone in the treatment of opioid dependence.

Materials and methods

Subjects

Ten adult male and female volunteers with heroin dependence were enrolled in the study. Recruitment of participants was performed by study staff, primarily through newspaper advertisements and responding to telephone inquiries. Inclusionary criteria included an age of 18–55 years, diagnosis of current opioid dependence as assessed using the Structured Clinical Interview for DSM-IV (First et al. 1995), and eligibility for (but not enrolled in) opioid agonist treatment. Exclusionary criteria included pregnancy and significant medical or non-substance use psychiatric illness (e.g., schizophrenia). Individuals seeking substance abuse treatment were not enrolled but were assisted in referral to community-based treatment programs.

Participants underwent routine medical screening, including medical history and physical examination, psychiatric history, electrocardiogram, and basic chemistry, hematology and urinalysis testing. Results were reviewed by medical staff not involved in the study as investigators, and all subjects were found to be without significant medical or psychiatric problems. The study was approved by the Institutional Review Board; volunteers gave written informed consent and were paid for their participation.

The first two participants were pilot safety subjects who were tested in a non-randomized escalating dose order to ensure all conditions would be tolerated. Otherwise, all procedures for these two subjects were identical to those used for the remaining eight subjects. Data from these first two participants are excluded from analyses.

The two pilot subjects tolerated all dose conditions, and the remaining eight participants were tested with randomized dose sequences. Of these eight subjects, six were male, all were African-American, and they had an average age of 36 years (range 27–45 years). The mean duration of illicit opioid use was 8.5 years (range 4–14 years), frequency of use was at least once per day, and amount spent on opioids ranged from $10 to over $150 per day.

Study setting

Subjects lived on a closed, 14-bed pharmacology residential research unit while participating in the study. Urine samples were collected at admission and intermittently throughout participation, and tested for the presence of illicit drugs using an EMIT system (Dade Behring, Inc.). Breathalyzer testing for alcohol was done on the day of admission and at least twice weekly. There was no evidence of unauthorized drug or alcohol use during study participation.

Study procedure

Participants were screened on an outpatient basis to determine study eligibility. Subjects who fulfilled inclusion and exclusion criteria were admitted and oriented to the residential unit, gave consent, and were introduced to the session room and the staff who would conduct the laboratory sessions. Participants were started on oral hydromorphone as a maintenance substitution therapy (10 mg four times per day). Hydromorphone was chosen due

to a pharmacologic and time-course profile that closely mirrors the pattern of use and the level of physical dependence observed with heroin. During the several days following admission, participants received training on the various tasks they would be required to perform. The first experimental session, a practice session, was scheduled at least 4 days after admission in order to achieve stabilization on hydromorphone and to rule out physical dependence on alcohol/sedatives.

Each subject participated in a minimum of 16 experimental sessions (including a training session) and typically resided on the unit for 10 weeks. After completion of the inpatient study, subjects were discharged to an outpatient treatment/research clinic where they were maintained on buprenorphine or buprenorphine/naloxone during participation in a pharmacokinetic study that will be reported separately. Subsequently, participants were assisted in enrolling in a drug treatment program, during which they could be transferred to methadone maintenance, or detoxified off opioids and transferred to a drug-free treatment program.

Laboratory sessions

Sessions were conducted at the same time of day, twice weekly, with at least 72 h between sessions. The session room contained a desk, two chairs, a Macintosh computer, and physiological monitoring equipment. Subject and observer questionnaires were presented on the computer screen, and responses were entered using a keypad and mouse.

Sessions lasted 3.5 h and were run by a research technician who was present throughout each session and blind to the drug and dose administered. During the first thirty minutes of each session, baseline physiological data were obtained, all subject and observer questionnaires were completed, and pupil photos were taken. Thirty minutes after the start of the session the participant was administered two intramuscular injections (one-half of the dose in each arm), followed by SL tablets. Injections were divided to prevent leakage and tissue damage due to the substantial volume of solution used. Before administration of SL tablets, the subject rinsed his/her mouth with water. The session then continued for 3 h, with data collected as described below.

In the first session for each subject, the drugs administered were saline IM injections and placebo SL tablets. This session followed the format of all subsequent sessions, including blindness of session staff to the drug administered; it served as a training session and was excluded from statistical analyses.

Session drugs and doses

Subjects were maintained on 40 mg per day of oral hydromorphone (10 mg, four times per day). Each dose of hydromorphone (10 mg) was provided in a size 0, opaque capsule loose-filled with five, 2 mg hydromorphone tablets (Knoll Pharmaceuticals, Mount Olive, N.J., USA) and lactose (Amend Drug and Chemical Company, Irvington, N.J., USA). Capsules were administered under nursing supervision at 6:00 a.m., 10:00 a.m., 4:00 p.m. and 8:00 p.m. on non-test session days, or at 6:00 a.m., 12:15 p.m. (post-session), 4:00 p.m. and 8:00 p.m. on test session days.

Fifteen experimental drug conditions were tested: placebo, hydromorphone 10 mg given by IM injection (an agonist control condition), naloxone 0.25 mg given by IM injection (an antagonist control condition), buprenorphine 8 mg given by IM injection, buprenorphine 8 mg given as SL tablet, and buprenorphine/naloxone combinations of 1/0.25, 2/0.5, 4/1, 8/2, and 16/4 mg, each given once by IM injection and once as SL tablets.

A commercial preparation of hydromorphone hydrochloride (10 mg/ml; Knoll Pharmaceuticals) was used for the IM hydromorphone dose condition.

The three lowest doses of naloxone for injection (0.25, 0.5 mg, and 1.0 mg) were prepared from commercial naloxone hydrochloride product (0.4 mg/ml and 1.0 mg/ml; DuPont Pharma, DuPont Merck Pharma, Manati, Puerto Rico), by diluting to the appropriate volume with bacteriostatic water for injection. The two higher doses of naloxone (2 and 4 mg) were prepared from naloxone powder (DuPont Pharmaceuticals, Wilmington, Del., USA), using bacteriostatic saline to make a 10 mg/ml stock solution. This stock solution was then diluted with bacteriostatic water in order to obtain the appropriate doses. Bacteriostatic water was used for placebo injections.

Buprenorphine was supplied by NIDA, Research Technology Branch (Rockville, Md., USA), from a supply provided by Reckitt and Colman (Hull, UK). Buprenorphine for injection was prepared as a stock solution from pure powder using doubly distilled water, and adjusted with hydrochloric acid to pH 4.0–4.5. This stock solution was then diluted using bacteriostatic water to obtain the appropriate concentrations.

Buprenorphine for SL administration was delivered as SL tablets that were of two sizes. Small tablets weighed 100 mg and contained either placebo, or 2 mg buprenorphine combined with 0.5 mg naloxone. Large tablets weighed 400 mg and contained placebo, 8 mg buprenorphine alone, or 8 mg buprenorphine combined with 2 mg naloxone. Tablets containing buprenorphine alone, buprenorphine combined with naloxone, and placebo were matched for color and taste.

During every session, subjects received, all at once, two large tablets and two and one-half small tablets in each session (combining active tablets with placebo tablets to maintain blinding of each dose). Each split tablet was weighed before being divided, and half-tablets were within ±5% of one-half the whole tablet's weight. The 1 mg buprenorphine plus 0.25 mg naloxone condition was delivered as one-half of one small tablet, and the 2 mg buprenorphine plus 0.5 mg naloxone condition was delivered as one small tablet. The 4 mg buprenorphine plus 1 mg naloxone condition was delivered as two small combination tablets. The 8 mg buprenorphine dose conditions (8 mg buprenorphine alone and 8 mg buprenorphine combined with 2 mg naloxone) were each delivered as one large tablet, and the 16 mg buprenorphine plus 4 mg naloxone condition was delivered as two large tablets.

The order of conditions for the sessions was derived from a Latin-square for thirty subjects. Subjects were assigned one of the schedules using a random number table.

Dosing procedures

On test session days, participants received their usual dose of hydromorphone at 6:00 a.m. Test drug administrations occurred at 9:00 a.m. (i.e., 3 h after the last dose of hydromorphone). Subjects received IM injections, rinsed their mouth with tap water, then received the SL tablets. Participants did not receive their usual 10:00 a.m. dose of hydromorphone until 12:15 p.m., when the experimental test session was complete.

Physiological measures

Heart rate, blood pressure, skin temperature, respiratory rate, and oxygen saturation were monitored throughout the session. All of these measures were collected using a Criticare Non-Invasive Patient Monitor (model 507S, Criticare Systems, Inc., Waukesha, Mich., USA). Skin temperature, respiratory rate, and oxygen saturation were recorded once per minute, and heart rate and blood pressure were recorded every third minute. The blood pressure cuff was placed on the subject's dominant arm. Skin temperature was monitored using a skin surface thermistor taped to the ring finger of the non-dominant arm, and the oxygen saturation clip was placed on the middle finger of the same arm. Data for each measure were collected and stored using a Macintosh computer (Apple Computer, Inc., Cupertino, Calif., USA), and averaged across time intervals: baseline (the 15-min interval from 15 min to 1 min before drug administration), and then 15-min intervals following drug administration (1–15, 16–30, 31–45,...151–165, and 166–180 min). Pupil diameter was determined from photographs taken in standardized ambient room lighting using a Polaroid cam-

era with ×2 magnification. Pupil photographs were taken three times 15 min before drug administration, and at 15, 30, 45, 60, 75, 90, 105, 120, 150, and 180 min after drug administration. The mid-value pre-drug pupil photo was used as the baseline measure.

Subject and observer measures

Subjective effect reports and observer rating questionnaires were completed 15 min before and at 15, 30, 45, 60, 75, 90, 105, 120, 150 and 180 min after drug administration. Subjects were instructed to respond describing how they felt at the time the questionnaire was answered.

Subjects completed visual analog scales and an adjective rating questionnaire. There were six visual analog scales: High, Drug Effects, Good Effects, Bad Effects, Liking, and Sick. Each scale was a horizontal line on the computer screen, and the subject positioned an intersecting vertical line along the horizontal line using the mouse. The ends of the horizontal line were labelled "None" and "Extremely," and responses were scored proportionately on a 100-point scale. The adjective rating questionnaire (Fraser et al. 1961; Jasinski 1977) consisted of 37 items which the participant rated on a five-point scale from 0 (not at all) to 4 (extremely); the items constituted two scales: a 16-item opioid Agonist scale (adjectives associated with morphine-like effects), and a 21-item Withdrawal scale (adjectives associated with opioid withdrawal-like effects). The items in the Agonist scale were: nodding, heavy/sluggish feeling, dry mouth, carefree, good mood, energetic, turning of stomach, skin itchy, relaxed, coasting, soapbox (talkative), pleasant sick, drive, drunken, friendly, and nervous. The items in the Withdrawal scale were: muscle cramps, flushing, painful joints, yawning, restless, watery eyes, runny nose, chills or gooseflesh, sick to stomach, sneezing, abdominal cramps, irritable, backache, tense and jittery, sweating, depressed/sad, sleepy, shaky (hands), hot or cold flashes, bothered by noises, and skin clammy and damp. The ratings for individual items were summed for total subjective agonist and withdrawal adjective rating scores.

Observer ratings, done at the same times as the subject ratings, were performed by a research assistant trained to assess signs and symptoms of opioid agonist and withdrawal effects. Observer ratings included the same adjective rating scale, scored in the same way. In addition, an observer-rated assessment of seven signs of opioid withdrawal (lacrimation, rhinorrhea, perspiration, piloerection, yawning, restlessness, and bowel sounds) was performed (derived from Kolb and Himmelsbach 1938). Each opioid withdrawal item was scored using standardized criteria, as 0, 1 or 2 (with higher scores corresponding to greater severity), and scores for all items were summed to produce a total observer Withdrawal Signs Score (WSS).

Psychomotor/cognitive performance measures

Subjects completed three psychomotor/cognitive performance tasks during the session: a computerized form of the Digit Symbol Substitution Task (DSST, McLeod et al. 1982), a Circular Lights task (Griffiths et al. 1983), and a computerized form of the Trail-Making Test (Strain et al. 2000). This latter test was a Macintosh-based version of the Trail-Making Test (Reitan 1958). In this task, the computer screen presented a distribution of squares that contained letters and numbers, and the subject was instructed to use a mouse to connect squares following an alternating sequence of numbers and letters (e.g., 1, A, 2, B, 3, C...). A total of 25 squares were presented (A-L and 1–13), and subjects had 4 min to complete the task. Results were summarized for sequence errors (i.e., clicking on a number or letter out of order), and the total line length. Each of the three tasks was completed during the baseline period (15 min before drug administration), and at the same time periods as subject ratings.

Data analysis

Peak values for each session were determined for each measure. For most measures this was an increased effect. However, since some measures may decrease in response to acute opioid agonist effects (e.g., pupil diameter, certain psychomotor tasks), the absolute nadir effect for these measures was examined.

A conservative one-step procedure, Tukey's honestly significant difference (HSD), was used to compare peak placebo values to the peak value of each active drug condition. The mean square error term needed to perform these tests was calculated using a repeated measures, two-factor analysis of variance; main effects were the fifteen drug conditions and time (baseline versus peak effect). Comparisons for which the Tukey q-value was greater than 5.487 ($P<0.05$) are reported as statistically significant.

Results

Table 1 summarizes mean values and results of post hoc analyses comparing peak drug effect to peak placebo effect for subjective, observer-rated, physiologic, and psychomotor measures obtained during the experimental sessions. Items shown had at least one condition that was significantly different from placebo.

Subjective effects

Mean peak visual analog scale ratings are presented in Fig. 1. Naloxone, the antagonist control condition, produced mild, non-significant increases in ratings of Drug Effects. Hydromorphone, the opioid agonist control condition, significantly increased ratings of Drug Effects, High, Good Effects, and Liking.

The effects of buprenorphine 8 mg (without naloxone) varied as a function of the route of administration. When given by injection, it significantly increased ratings of Drug Effects, High, Good Effects, and Liking. This pattern and the magnitude of effects were similar to that seen with hydromorphone (which was also given by injection). When buprenorphine 8 mg was given by the SL route, the magnitude of ratings was virtually identical to that produced by the placebo condition.

The combination of buprenorphine/naloxone when given by the IM route produced dose-related increases in ratings of Drug Effects, Bad Effects, and Sick. For the higher doses of IM buprenorphine/naloxone (4/1–16/4 mg), these ratings significantly differed from placebo. Intramuscular buprenorphine/naloxone produced mild, non-significant increases on measures suggestive of opioid agonist effects (High, Good Effects, Liking). The pattern for these measures appeared to be bell-shaped – that is, increased scores over the low-moderate dose range followed by decreased scores with the higher doses. However, none of these opioid agonist-like ratings was significantly different from placebo, and all were markedly lower than the corresponding ratings for the IM dose of buprenorphine alone.

When given by the SL route these same five doses of buprenorphine/naloxone produced a different pattern of effects on VAS ratings (Fig. 1). Sublingual buprenorphine/naloxone produced neither opioid antagonist-like

Table 1 Summary of peak drug effects. Values shown are the mean peak response (n=8). All doses shown are in milligrams. For subjective measures, observer-rated measures, diastolic and systolic blood pressure, heart rate, and Trails, the maximum positive increase was examined. For oxygen saturation and circular lights, the maximum decrease was examined. For pupil diameter, results are shown for both the maximum increase (max ↑) and the maximum decrease (max ↓), since pupillary response could vary in either direction as a function of opioid antagonist versus agonist challenge. *SL* sublingual, *IM* intramuscular, *N* naloxone, *H* hydromorphone

	Placebo	N(IM) 0.25	H(IM) 10	Buprenorphine		Buprenorphine/naloxone (IM)					Buprenorphine/naloxone (SL)				
				8 (IM)	8 (SL)	1/.25	2/.5	4/1	8/2	16/4	1/.25	2/.5	4/1	8/2	16/4
Subjective measures															
Visual analog scales															
High	6.1	14.0	43.1**	38.5**	7.9	7.1	17.1	17.4	21.6	12.4	6.6	0.3	0.5	13.3	14.5
Drug effects	8.8	27.3	47.3**	38.6**	10.0	16.4	20.1	31.3	42.9**	60.9**	9.9	5.6	6.8	14.4	13.0
Good effects	6.3	10.6	47.4**	37.3**	8.4	5.3	15.4	20.1	16.1	8.6	6.4	2.0	0.4	14.0	13.6
Bad effects	6.4	18.5	5.4	9.1	7.0	12.0	16.9	29.3*	43.4**	59.0**	3.5	5.9	6.6	0.3	0.0
Liking	3.0	9.6	48.4**	37.0**	8.0	3.5	23.6	19.1	18.8	5.8	6.4	0.3	0.0	14.4	14.5
Sick	6.1	19.0	2.4	8.4	0.0	10.1	12.3	23.0	35.0**	59.8**	0.0	5.9	0.0	0.3	0.9
Adjective rating scales															
Agonist	13.6	12.1	19.6**	16.9*	14.6	13.6	13.1	14.1	13.9	13.3	13.0	11.9	12.9	14.0	14.5
Withdrawal	2.9	5.8	2.0	2.1	1.9	5.5	4.6	9.0*	10.6**	19.0**	2.4	4.8	3.9	1.5	1.6
Observer-rated measures															
Adjective rating scales															
Agonist	11.9	10.4	20.0**	15.3	13.1	11.5	13.5	12.1	12.9	11.5	12.9	10.0	11.8	13.4	13.8
Withdrawal	3.3	6.5	0.9	2.4	1.5	4.3	5.4	7.5	9.4*	17.5**	2.6	3.9	2.0	1.0	1.3
Withdrawal Signs Score	4.5	4.9	2.6	2.5	2.9	4.1	4.8	5.8	7.0	9.1**	3.8	4.4	3.0	2.8	2.5
Physiologic measures															
Diastolic blood pressure	69.6	72.8	75.7	71.2	70.9	74.0	74.1	75.0	76.9*	81.3**	73.0	70.9	71.2	71.2	73.8
Systolic blood pressure	123.6	130.3	128.4	127.2	127.2	127.3	130.7	133.0	134.2	139.4**	126.4	125.9	127.2	126.9	129.9
Heart rate	76.6	79.5	84.2**	80.6	79.7	79.6	78.9	80.8	85.0**	84.4**	78.6	77.0	78.6	77.9	79.5
Pupil diameter (max ↑)	5.5	5.3	3.9	4.3	4.9	5.1	5.3	5.4	5.5	5.7	5.1	4.9	5.0	4.9	5.0
Pupil diameter (max ↓)	3.9	3.5	2.7**	3.2	3.3	3.5	3.9	3.4	3.4	3.2	3.9	3.7	3.7	3.5	3.7
Oxygen saturation	97.8	98.0	96.8**	97.1*	97.6	97.4	97.5	97.4	97.2	97.4	97.8	97.5	97.7	97.4	97.5
Psychomotor tasks															
Circular lights	71.4	65.8	56.3**	61.1	70.4	66.3	66.6	61.8	64.0	55.6**	69.9	65.9	70.8	67.5	66.5
Trails (sequence errors)	2.8	3.3	4.9	4.8	3.8	3.4	3.9	4.6	9.5**	9.9**	2.4	4.0	4.8	6.4	3.1

*P<0.05; **P<0.01 versus placebo

effects nor opioid agonist-like effects as measured by these visual analog scale ratings. For all six of the visual analog scales, SL buprenorphine/naloxone produced low ratings with no clear dose-related pattern, and no significant differences from placebo.

Results from the subject adjective rating questionnaire showed that hydromorphone and IM buprenorphine 8 mg both produced significant increases on the Agonist scale score (Table 1). None of the ten buprenorphine/naloxone conditions produced significant increases in Agonist scale scores, and the mean scores for the IM versus SL routes were generally in the same range. Finally, consistent with the pattern seen for the visual analog scales, the subject adjective rating scale scores for Withdrawal showed significantly increased scores for each of the three highest doses of IM buprenorphine/naloxone (4/1–16/4 mg; Table 1).

Observer-rated effects

Only the hydromorphone condition produced scores on the adjective Agonist scale completed by the trained observer that were significantly higher than placebo scores (Table 1). Peak scores on the observer adjective Agonist scale for the ten buprenorphine/naloxone conditions showed no pattern suggestive of dose-related effects for either the IM or SL conditions.

Peak scores for the observer adjective Withdrawal scale showed dose-related increases for the IM buprenor-

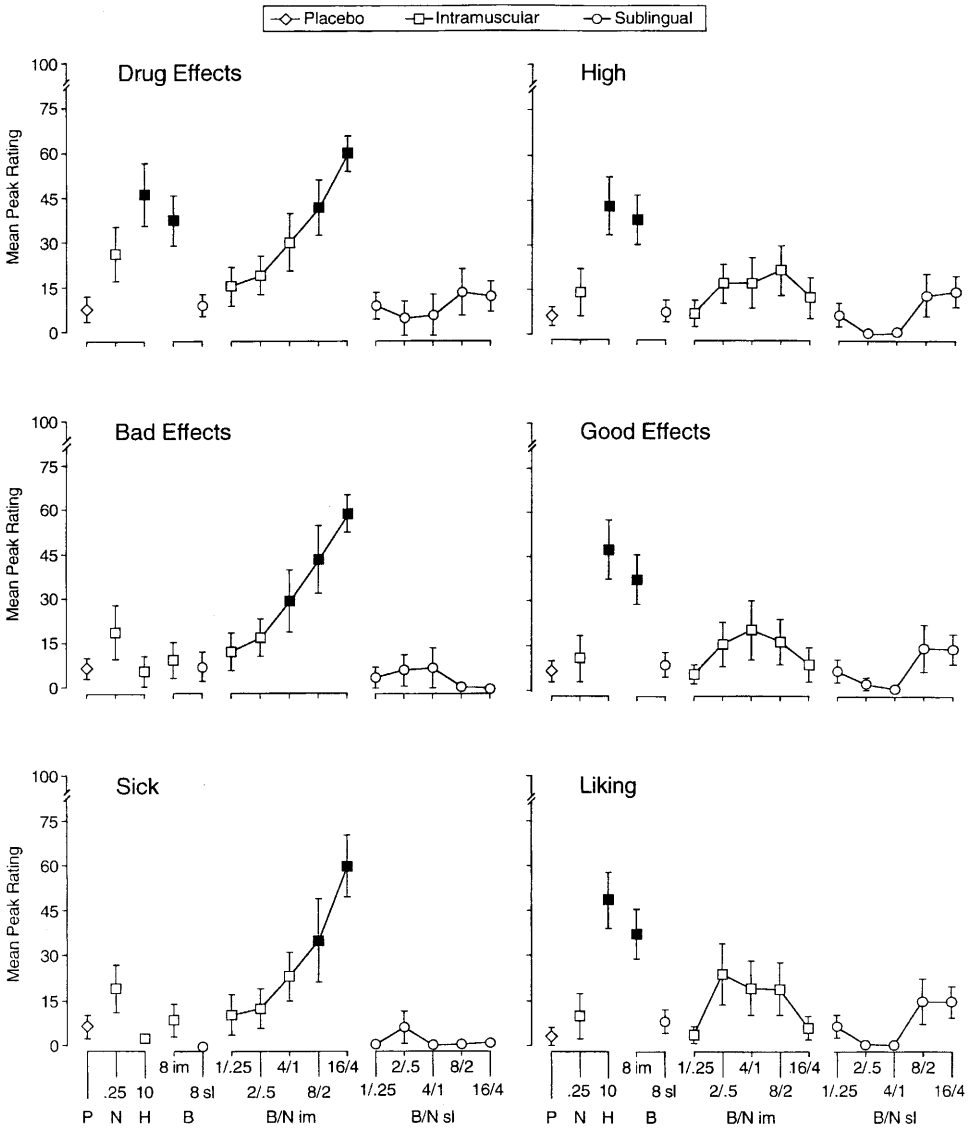


Fig. 1 Mean peak values (±SE) for subject-reported visual analog scale ratings (n=8 subjects). Acute dosing conditions are shown along the x-axis as placebo (*P*), naloxone (*N*), hydromorphone (*H*), buprenorphine (*B*), and buprenorphine/naloxone (*B*/*N*). All doses shown are in mg. Route of administration: *im* intramuscular, *sl* sublingual. The maximum possible score was 100. Conditions which differed significantly from placebo (Tukey test; $P<0.05$) are indicated by *filled symbols*

phine/naloxone conditions, with significant elevations for the two highest doses tested (Table 1). None of the other drug conditions produced significant effects for this measure. A similar pattern was seen for the observer Withdrawal Signs Score (WSS), with dose-related increases for the five IM buprenorphine/naloxone conditions (Table 1); only the highest dose tested (16/4 mg) was significantly higher than placebo. None of the other drug conditions tested produced significant WSS effects in comparison to placebo.

The mean peak scores for individual items from the WSS are shown for the placebo, naloxone, and the IM buprenorphine/naloxone conditions in Fig. 2. (The item "bowel sounds" is not shown, since peak ratings were consistently 2 for all subjects and all dose conditions.) As can be seen in Fig. 2, for most items the IM buprenorphine/naloxone conditions produced dose-related increases in scores, with higher doses producing significantly elevated scores for several items (Perspiration, Piloerection, and Restlessness). Significant withdrawal effects were observed only when the buprenorphine/naloxone combination delivered IM naloxone doses of 2 mg or more. Interestingly, naloxone 0.25 mg alone did not produce significant changes for individual items or the total WSS scores (Table 1 and Fig. 2).

Neither buprenorphine alone (8 mg IM or SL) nor SL buprenorphine/naloxone showed any suggestion of increasing withdrawal signs. Rather, their trend was to reduce withdrawal signs; this achieved statistical significance for the 8 mg IM buprenorphine condition, which significantly decreased scores on Yawning (as did the IM hydromorphone condition and the two highest doses of SL buprenorphine/naloxone; not shown in Fig. 2).

Physiologic effects

None of the dose conditions tested produced significant changes on measures of respiratory rate. Diastolic blood pressure was significantly elevated for the two highest

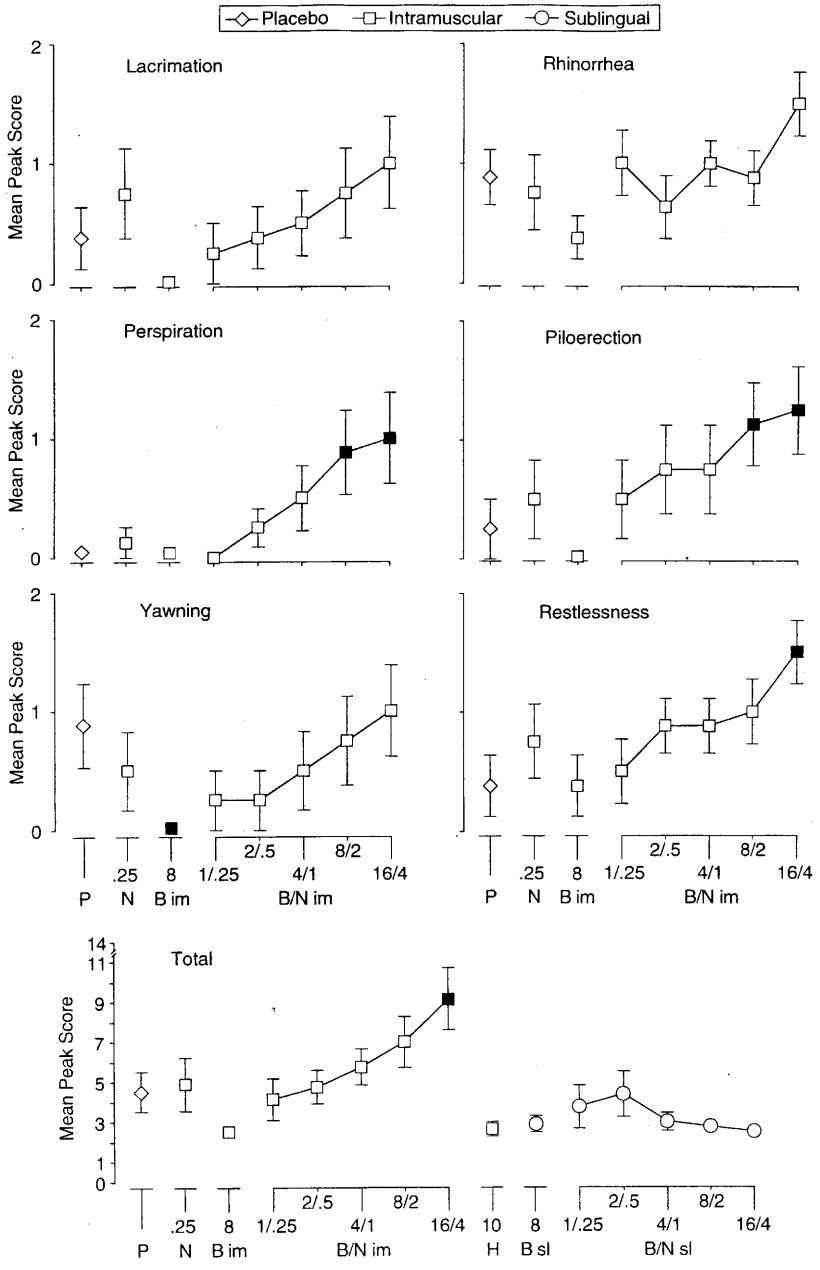
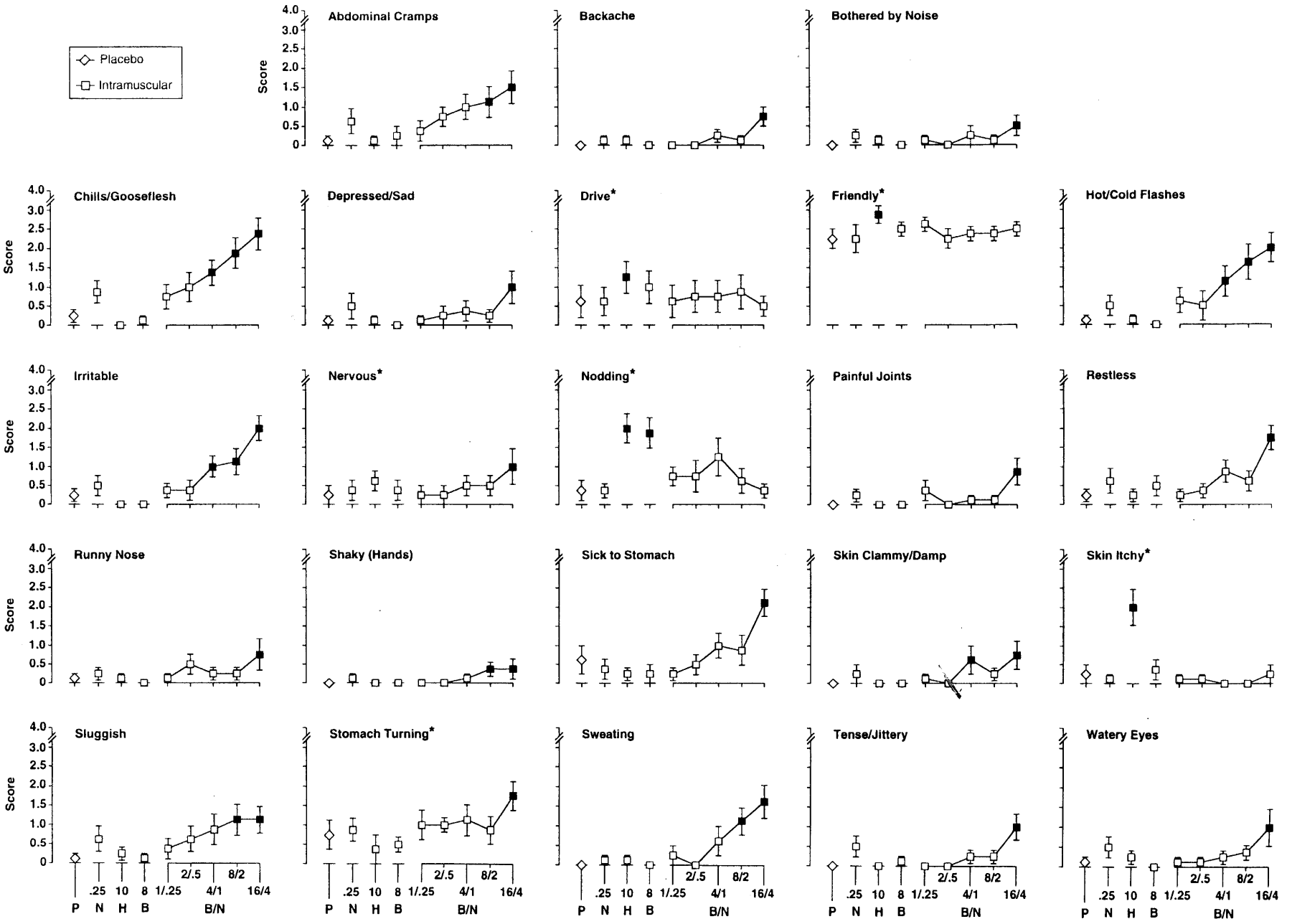


Fig. 2 Observer ratings of opioid withdrawal signs, effects of acute doses of placebo (*P*), naloxone (*N*), IM buprenorphine (*B*) and IM buprenorphine/naloxone (*B/N*). The individual items for SL conditions are not shown because there were no significant effects. All doses shown are in mg. Route of administration: *im* intramuscular, *sl* sublingual. The maximum possible score for each individual item was 2. Total score is the sum of all items. Each point (and bracket) is the mean peak score (±SE) for eight subjects. Where no bracket is shown, the SE is smaller than the diameter of the symbol. Scores for bowel sounds are not shown, as ratings were consistently two for all subjects and all dose conditions. Conditions which differed significantly from placebo (Tukey test; $P<0.05$) are indicated by *filled symbols*

doses and systolic blood pressure was significantly elevated for the highest dose of the IM buprenorphine/naloxone condition (Table 1). These elevations, while significantly higher than placebo, were generally of mild degree and not clinically significant (with the maximum mean blood pressure being 139/84). None of the other drug conditions produced significant changes on peak diastolic or systolic blood pressures. Heart rate was significantly elevated for the hydromorphone condition, and the two highest doses of IM buprenorphine/naloxone. However, like blood pressure changes, these increases in heart rate were mild (less than a 10 bpm increase relative to placebo), and not clinically significant.

Fig. 3 Individual adjective items from the subject-reported adjective rating questionnaire, effects of acute doses of placebo (*P*), naloxone (*N*), hydromorphone (*H*), IM buprenorphine (*B*), and IM buprenorphine/naloxone (*B/N*). All doses are shown in mg. Each point (and bracket) represents the mean peak score (±SE) for the eight subjects. Where no bracket is shown, the SE is smaller than the diameter of the symbol. Items excluded from the figure had no conditions that differed significantly from placebo. The SL conditions are not shown because of a lack of significant effects. Conditions which differed significantly from placebo (Tukey test; $P<0.05$) are indicated by *filled symbols*. *Asterisks* indicate items scored on the agonist scale; all other items are scored on the antagonist scale ▶


Placebo
Intramuscular
Score
Abdominal Cramps
Backache
Bothered by Noise
Chills/Gooseflesh
Depressed/Sad
Drive*
Friendly*
Hot/Cold Flashes
Irritable
Nervous*
Nodding*
Painful Joints
Restless
Runny Nose
Shaky (Hands)
Sick to Stomach
Skin Clammy/Damp
Skin Itchy*
Sluggish
Stomach Turning*
Sweating
Tense/Jittery
Watery Eyes
4.0
3.0
2.5
2.0
1.5
1.0
0.5
0
P
N
.25
H
10
B
8
1/.25
2/.5
4/1
8/2
16/4
B/N

Since changes in pupil diameter can vary depending upon whether an opioid-dependent person is challenged with an opioid agonist (which may produce pupillary constriction) or an opioid antagonist (which may produce pupillary dilation), results in Table 1 are shown for both maximum pupillary dilation and constriction. None of the drug conditions tested produced significant pupillary dilation relative to placebo (Table 1), but the hydromorphone condition produced significant pupillary constriction.

Finally, two drug conditions produced significant effects on oxygen saturation. Both the hydromorphone condition and the 8 mg IM buprenorphine condition significantly decreased oxygen saturation, an index of respiratory depression (Table 1). None of the other conditions produced significant effects on oxygen saturation.

Psychomotor effects

There were no significant effects of any test condition on the Trails total line length or total errors, or on DSST number attempted, number correct, or percent errors (not shown in Table 1). Circular lights performance, an index of gross motor skill and hand-eye coordination, was decreased by IM hydromorphone and by the highest dose of IM buprenorphine/naloxone (Table 1). There was also a significant increase in the number of Trails sequence errors, an index of information processing, for the two highest doses of IM buprenorphine/naloxone.

There was no evidence that SL buprenorphine/naloxone impaired psychomotor performance.

Individual adjective items

Results from analyses of subject individual adjective item peak scores are shown in Fig. 3. Items for which at least one dose condition significantly differed from placebo are shown in this figure. None of the SL dose conditions produced significant effects, and hence are not shown in the figure.

In general, the IM buprenorphine/naloxone conditions produced dose-related increases on items typical of opioid withdrawal effects (e.g., chills/gooseflesh, sick to stomach, hot/cold flashes). The dose at which effects appeared varied across items, but for most items significant withdrawal effects did not occur until the 16/4 mg dose (although significant effects did occur with doses as low as 4/1 mg). None of the doses of the IM buprenorphine/naloxone conditions produced significant opioid agonist-like effects.

Hydromorphone and the IM buprenorphine alone condition increased scores significantly on items typical of opioid agonist effects (e.g., nodding, friendly, skin itchy), and did not significantly increase peak ratings on opioid withdrawal items. Naloxone did not produce significant changes on any items. Naloxone effects were mild and with scores similar to those produced by placebo.

Time course effects

Examples of time course effects for four measures – subjects' visual analog scale ratings of Bad Effects and Good Effects, and the physiologic measures pupil diameter and skin temperature – are shown in Fig. 4. The first three columns show results for the three highest buprenorphine/naloxone doses administered by each route (IM and SL), as well as placebo. The fourth column (far right) contains the control conditions (placebo, hydromorphone and naloxone) as well as the two buprenorphine 8 mg alone conditions. Ratings for the two lowest buprenorphine/naloxone doses tested showed minimal change over time, and thus are not included in the figure.

Intramuscular injection of naloxone (alone or in combination with buprenorphine) tended to produce rapid-onset ratings of Bad Effects, with peak effects occurring within 15–30 min post-injection. The magnitude of these effects was an increasing function of naloxone dose. With IM naloxone 0.25 mg alone the ratings were mild, though consistently higher than those produced by the corresponding buprenorphine/naloxone 1/0.25 mg condition (not shown in Fig. 4). The IM naloxone effects were relatively short-lived, declining quite substantially by 75 min post-injection. Although buprenorphine-alone effects were of substantially longer duration, there was little or no suggestion of any substantial increase in ratings of Good Effects as the naloxone wore off.

In the absence of naloxone, IM injection of hydromorphone or buprenorphine increased Good Effects ratings. The onset-slope of these Good Effects Ratings was shallower than for the Bad Effects ratings produced by conditions containing naloxone. The onset-slope for buprenorphine tended to be shallower than that for hydromorphone. The duration of the elevated Good Effects ratings for hydromorphone and buprenorphine was substantially longer than the duration of the naloxone-related elevations of Bad Effects ratings, persisting through 180 min post-injection.

In the absence of injection (i.e., when given sublingually) both buprenorphine alone and all the buprenorphine/naloxone combinations produced very modest effects of gradual onset, and similar to ratings of placebo.

The bottom two rows in Fig. 4 show the physiological indices of pupil diameter and skin temperature. Both showed biphasic effects under the IM buprenorphine/naloxone combination conditions, with an initial effect indicative of a withdrawal-like naloxone action (pupillary diameter increase and skin temperature decrease peaking at 15–30 min post-injection) followed by a longer duration opioid agonist-like effect (pupil diameter decrease and skin temperature increase) that persisted through the remainder of the session. In the absence of injected naloxone only agonist-like effects occurred. The magnitude of the withdrawal-like effects appeared positively related to the IM naloxone dose. The overall peak magnitudes of agonist-like effects were similar for IM and SL buprenorphine.

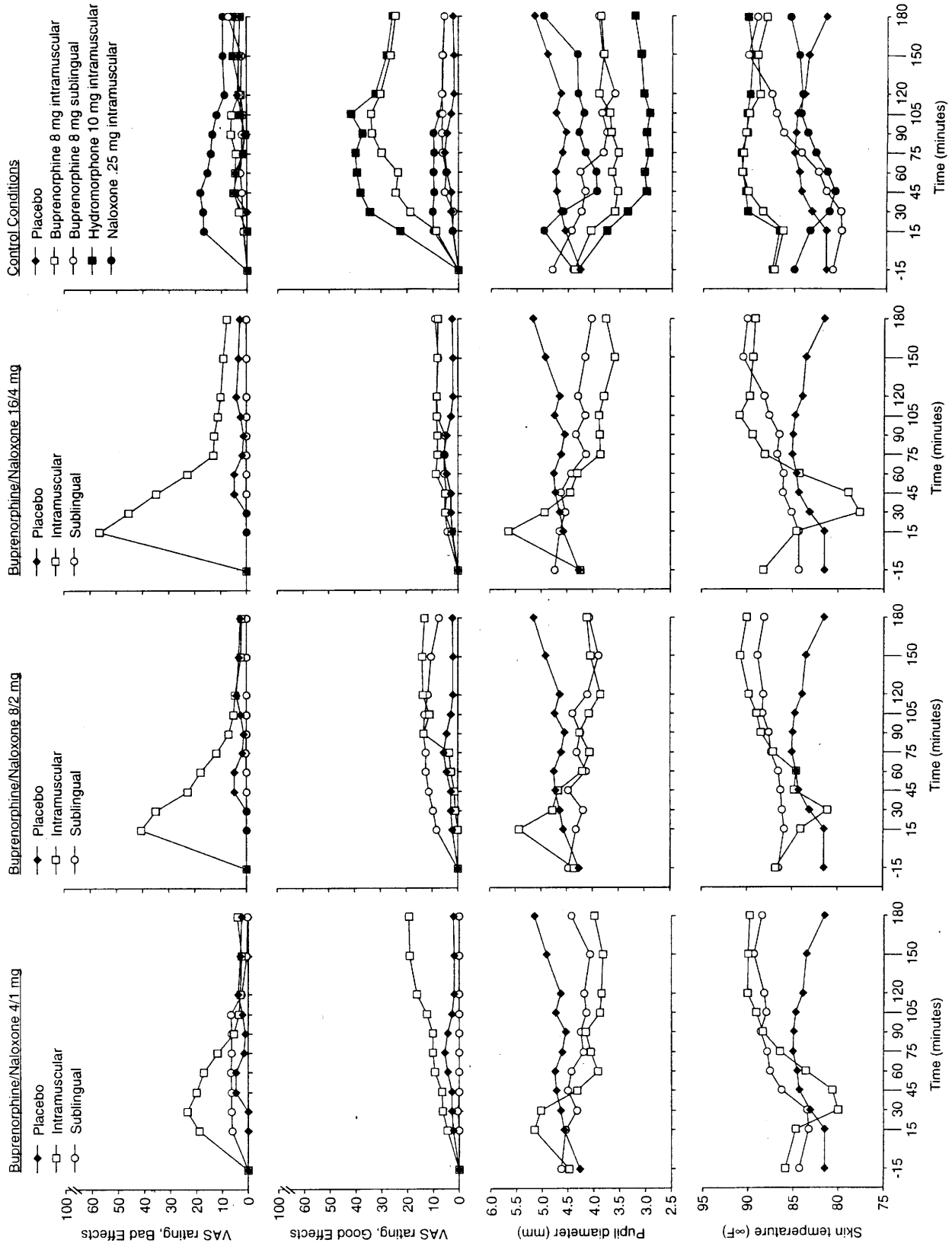


Fig. 4 Time course of effects for subject-reported visual analog scale (*VAS*) ratings of Bad Effects and Good Effects, and the physiological measures pupil diameter and skin temperature (see y-axes). Each point represents the mean value for the eight subjects at that time. The IM and SL buprenorphine/naloxone 1/0.25 mg and buprenorphine/naloxone 2/0.5 mg conditions were excluded due to a lack of robust drug response for those conditions

Discussion

This study evaluated the effects of buprenorphine/naloxone combinations in opioid dependent volunteers. The results show that this combination produced dose-related opioid antagonist effects when administered by injection, but that the same doses produced neither significant opioid antagonist nor agonist effects when administered by the SL route. These effects are consistent with the desired therapeutic profile of buprenorphine/naloxone – that is, adverse effects if injected, but low abuse potential and no adverse effects if taken by the therapeutic SL route.

There were two active control conditions in this study: hydromorphone and naloxone, each administered by IM injection. Hydromorphone produced effects consistent with its characterization as a prototypic mu opioid agonist. That is, subjects reported significant increases on ratings of High, Good Effects and Liking on visual analog scales (Fig. 1), and significant increases for the Agonist adjective rating scale (Table 1). Observer ratings were consistent with this opioid agonist pattern, and physiologic indices also showed significant opioid agonist-like changes for hydromorphone (e.g., pupillary constriction; Table 1).

The naloxone control condition of 0.25 mg by injection was selected so that comparison could be made to the buprenorphine/naloxone condition of 1/0.25 mg given by injection (i.e., to determine how buprenorphine might alter the effects of this dose of naloxone). This dose of naloxone was also selected based upon earlier studies of naloxone challenges in methadone-maintained volunteers receiving 30–60 mg oral methadone per day. In these studies, parenteral naloxone doses of 0.1–0.2 mg produced significant elevations on opioid withdrawal measures (e.g., Preston et al. 1988; Mendelson et al. 1997). In the present study, naloxone did not significantly increase ratings on measures typically associated with opioid withdrawal effects. Notably, this was not due to insensitivity to opioid withdrawal on the part of the subjects in the study; when challenged with higher-dose buprenorphine/naloxone combinations by injection, robust and significant withdrawal effects were produced. The lack of a precipitated withdrawal syndrome by the 0.25 mg naloxone condition may reflect the relatively low level of physical dependence for subjects in this study.

Challenges with buprenorphine/naloxone produced markedly different responses when given by the IM versus SL routes. In general, IM buprenorphine/naloxone produced dose-related antagonist-like effects, as assessed by subject, observer, and physiological measures (e.g., Table 1, Figs. 1 and 2). Antagonist-like effects from IM buprenorphine/naloxone were especially prominent for the two highest doses tested.

These adverse effects associated with IM buprenorphine/naloxone had a rapid onset and short duration (Fig. 4, first row). Subjective reports of antagonist-like effects typically began in the first 15 min after injection, and started to decline within the first 30 min after injection. The time course of these effects is consistent with the pharmacokinetic profile of naloxone. While antagonist effects were diminishing within the hour after injection, no increase in opioid agonist-like effects was seen on subjective measures (Fig. 4). That is, there was no evidence that buprenorphine agonist effects were reported as naloxone effects dissipated.

Interestingly, a previous study, in which buprenorphine combined with naloxone was given intravenously in a 1:1 dose ratio (i.e., 2/2 mg) to opioid dependent volunteers, showed some evidence that opioid agonist effects can appear as naloxone antagonist effects dissipate (Mendelson et al. 1996). In that study the onset of agonist-like effects occurred between 15 and 30 min post-dose, with peak effects within 2–3 h post-dose. However, studies in which opioid dependent subjects received intravenous buprenorphine/naloxone in ratios of 2:1, 4:1 and 8:1 (with the dose of buprenorphine always 2 mg) did not show agonist effects (Fudala et al. 1998; Mendelson et al. 1999). These differences across studies in the appearance and relative intensity of agonist and antagonist effects in response to parenteral doses of buprenorphine/naloxone probably reflect different levels of physical dependence in study populations, as well as the use of different maintenance medications, differing time intervals between maintenance medication and injected buprenorphine/naloxone, and different dose ratios of buprenorphine/naloxone.

In order to assess further the effects of injected buprenorphine/naloxone, individual items from the subject-rated adjective checklist and the observer-rated Withdrawal Signs were examined. The Withdrawal Signs assessment showed that scores generally increased as a function of buprenorphine/naloxone dose given by injection (Fig. 2), with significant peak scores noted on some items for the highest two doses tested. All items from the Withdrawal Signs assessment (except bowel sounds) appeared to be sensitive to detecting effects of IM buprenorphine/naloxone.

Individual subject-rated adjective items showed a variable pattern for IM buprenorphine/naloxone, and unlike the Withdrawal Signs assessment not all items appeared to be sensitive to detecting antagonist effects of IM buprenorphine/naloxone (Fig. 3). For some items, scores increased as a function of dose, in a pattern consistent with the Withdrawal Signs scores (e.g., irritable, chills/gooseflesh). For other items, a less discernable pattern was evident (e.g., skin clammy/damp, painful joints). However, as with the Withdrawal Signs items, it was the higher doses of buprenorphine/naloxone given by injection that produced significant scores. In addition, hydromorphone and buprenorphine alone (by injection) also produced significant elevations on some items associated with opioid agonist effects (e.g., nodding, skin itchy).

In contrast to the multiple significant effects produced by IM buprenorphine/naloxone, SL buprenorphine/naloxone produced neither agonist-like nor antagonist-like

effects. The lack of antagonist effects for higher doses of SL buprenorphine/naloxone is somewhat surprising, since SL doses of naloxone alone of this magnitude (up to 4 mg) can precipitate withdrawal in opioid-dependent subjects (Preston et al. 1990). One possible explanation for this absence of antagonist effects by high doses of SL buprenorphine/naloxone, is that SL naloxone's potential antagonist effects are offset by buprenorphine's agonist effects. Alternatively, a low level of physical dependence for subjects in this study, as suggested by the lack of significant precipitated withdrawal by the 0.25 mg naloxone condition, may contribute to this finding.

The inclusion of buprenorphine without naloxone in this study allows a further characterization of the relative effects of adding naloxone to buprenorphine. For example, it is possible to compare injected buprenorphine (8 mg) alone and when combined with 2 mg naloxone. As a partial agonist opioid, buprenorphine alone can demonstrate either opioid agonist or antagonist properties under the proper experimental conditions; precipitated withdrawal in opioid dependent subjects has been induced with buprenorphine (Strain et al. 1995; Walsh et al. 1995). In the present study, IM buprenorphine alone did not precipitate withdrawal, but produced opioid agonist-like effects (Table 1). Under conditions in which subjects have a low level of physical dependence, it is expected that buprenorphine would demonstrate agonist effects, consistent with the results seen in this study.

In contrast to the agonist effects of injected 8 mg buprenorphine alone, the 8/2 mg dose of IM buprenorphine/naloxone produced no significant increases in opioid agonist ratings, although it did produce significant changes in measures of opioid antagonist effects (Table 1). The onset of agonist effects for 8 mg IM buprenorphine was slower than the onset of antagonist effects seen with 8/2 mg of IM buprenorphine/naloxone (top row of panels in Fig. 4), although the eventual magnitude of these effects was quite similar.

A comparison of 8 mg of buprenorphine by SL administration to 8/2 mg of buprenorphine/naloxone sublingually shows the two conditions were virtually identical in their magnitude and time course of ratings (Table 1, Figs. 1 and 4). These minimal and non-significant effects of buprenorphine and buprenorphine/naloxone by the SL route illustrate the low abuse potential of these formulations when taken therapeutically by opioid maintained persons. Further, the absence of opioid agonist effects with buprenorphine alone given sublingually, but the elicitation of opioid agonist effects by buprenorphine alone given by injection, illustrates how a tablet containing buprenorphine alone has a low abuse potential when taken by the prescribed route, but could be abused if dissolved and injected. However, it should be noted that there may be an abuse potential in populations not physiologically dependent on opioids (e.g., Strain et al. 2000).

In addition to subject and observer ratings of drug effects, this study also assessed physiological and psychomotor changes associated with the experimental conditions (Table 1). In general, effects in these areas were consistent with the subject and observer ratings. Thus, conditions that produced opioid agonist-like effects on subject and observer measures (hydromorphone, IM buprenorphine without naloxone) also produced pupillary constriction and decreases in oxygen saturation. However, while subject and observer measures did not show a delayed opioid agonist effect for IM buprenorphine/naloxone conditions, the time course of physiologic measures such as pupil diameter and skin temperature did show evidence of such an effect (Fig. 4, bottom two rows).

Impairments in psychomotor performance were seen on selected measures and with selected conditions (Table 1). The highest dose of IM buprenorphine/naloxone significantly decreased the number of responses on the circular lights task (a measure of gross motor function), as did the hydromorphone condition. The two highest doses of IM buprenorphine/naloxone also significantly increased the number of sequence errors in the Trails test (a measure of information processing and finer motor skills). Mild impairments in psychomotor performance have also been shown with higher doses of SL buprenorphine/naloxone in non-dependent opioid abusers (Strain et al. 2000). The psychomotor performance changes in the present study were not dramatic, and suggest relatively little clinically significant impairment.

In summary, this study assessed the acute effects of buprenorphine/naloxone combinations in opioid dependent volunteers, when delivered either by the SL route or by injection. When buprenorphine/naloxone was given by injection, doses as low as 4/1 mg produced significant increases in measures of opioid antagonist effects, indicating a predominant naloxone effect which the concurrent administration of buprenorphine does not remove. This suggests a low abuse potential by the injection route for buprenorphine/naloxone in an opiate dependent population. When buprenorphine/naloxone was given sublingually, neither opioid antagonist nor agonist effects were produced, demonstrating a low abuse potential for the combination product when taken by the SL route in this population. Finally, the opioid antagonist effects of injected buprenorphine/naloxone appear to be attributable to naloxone, rather than to buprenorphine's partial agonist feature, since no evidence of precipitated withdrawal was seen when buprenorphine was administered alone. Together, the results from this and other studies of buprenorphine/naloxone provide further evidence supporting the development of buprenorphine and buprenorphine/naloxone combinations for the treatment of opioid dependence.

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