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ORIGINAL INVESTIGATION

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Effects of buprenorphine versus buprenorphine/naloxone tablets in non-dependent opioid abusers

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Abstract *Rationale:* Buprenorphine is an opioid agonist-antagonist under development in the United States as a sublingual medication for treatment of opioid dependence. Buprenorphine may be abused; therefore, tablets combining buprenorphine with naloxone have been developed with the intent of reducing the abuse risk in people physically dependent upon opioids. The characteristics and abuse potential of buprenorphine and buprenorphine/naloxone tablets in non-dependent opioid abusers have not been determined. Non-parenteral abuse of opioids such as buprenorphine may be more likely in people who have less severe substance abuse disorders (e.g., are not physically dependent upon opioids). *Objectives:* To assess the abuse potential of sublingual buprenorphine and buprenorphine/naloxone tablets in non-dependent opioid abusers. *Methods:* Subjects (n=7) were tested with sublingual buprenorphine (4, 8, 16 mg), sublingual buprenorphine/naloxone (1/0.25, 2/0.5, 4/1, 8/2, 16/4 mg), as well as intramuscular hydromorphone as an opioid agonist control (2, 4 mg) and placebo in laboratory sessions conducted twice per week. Dosing was double-blind and double-dummy. *Results:* The higher doses of both buprenorphine and buprenorphine/naloxone produced similar opioid agonist-like effects. The onset of these effects was slowed, consistent with the sublingual route of administration, and the magnitude of effects was moderate. There was no evidence to suggest the addition of naloxone attenuated buprenorphine's opioid agonist effects in this population when buprenorphine was delivered by the sublingual route. *Conclusions:* These results suggest that sublingual buprenorphine and buprenorphine/naloxone may both be abused by opioid users who are not physically dependent upon opioids.

Key words Agonist-antagonist · Buprenorphine · Buprenorphine/naloxone · Hydromorphone · Naloxone · Opioid abuse

Introduction

Buprenorphine is an opioid agonist-antagonist marketed worldwide as an analgesic. It is under development as a medication for the treatment of opioid dependence in the United States, and is already marketed for that use in France. Buprenorphine's pharmacologic profile suggests it should be an effective medication for the treatment of opioid dependence. Studies in humans have shown that acute doses of intravenous, sublingual, and subcutaneous buprenorphine are identified as opioid agonist-like (Jasinski et al. 1978, 1989; Johnson et al. 1989; Pickworth et al. 1993). In humans physically dependent on opioids, chronic buprenorphine dosing produces cross-tolerance to other opioids (Bickel et al. 1988a; Rosen et al. 1994) and can suppress self-administration of heroin by heroin abusers (Mello et al. 1982).

Buprenorphine is as a mu opioid partial agonist and a kappa antagonist (Rothman et al. 1995) that has been shown to have a bell-shaped dose-response curve. This bell-shaped dose-response curve suggests advantages and disadvantages in buprenorphine's use for the treatment of opioid dependence. For example, one advantage is that a buprenorphine overdose should not produce significant respiratory depression, and there is evidence to suggest that this is the case (Banks 1979; Walsh et al. 1994). However, a disadvantage is that there may be a plateau in the cross-tolerance produced by buprenorphine, so that increasing daily doses may not result in further clinical improvements.

Several outpatient clinical trials have tested the efficacy of buprenorphine in the treatment of opioid dependence. Most of these studies have compared buprenor-

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phine to methadone (Bickel et al. 1988b; Johnson et al. 1992; Kosten et al. 1993; Strain et al. 1994; Ling et al. 1996; Schottenfeld et al. 1997), although one clinical trial has compared buprenorphine to placebo (Johnson et al. 1995), and another compared buprenorphine to an active placebo (Ling et al. 1998). In general, these studies suggest that buprenorphine is an effective medication for the outpatient treatment of opioid dependence, and that sublingual doses of 8 mg buprenorphine daily are approximately equivalent to 50–60 mg oral methadone daily.

Because buprenorphine is a mu partial agonist opioid, it does have the potential to be abused. Indeed, there have been reports of buprenorphine abuse (Strang 1985; O'Connor et al. 1988; Gray et al. 1989; Singh et al. 1992; Robinson et al. 1993). Buprenorphine has poor bioavailability by the oral route, so formulations for the treatment of opioid dependence have needed to be water soluble and delivered sublingually. Early studies have used a sublingual solution, while more recent studies have used sublingual tablets. Since buprenorphine can be abused, these sublingual formulations have the potential to be injected.

In order to address this abuse potential, interest in buprenorphine's development has shifted to the creation of a combination product containing buprenorphine and naloxone. Naloxone has poor sublingual bioavailability (Preston et al. 1990), so use of such tablets by the therapeutic sublingual route should produce a predominantly buprenorphine effect. However, if buprenorphine/naloxone tablets were dissolved and injected by an opioid-dependent person, then the naloxone should produce a precipitated withdrawal syndrome. Indeed, studies of buprenorphine combined with naloxone and parenterally administered to opioid-dependent volunteers have shown that the addition of naloxone precipitates withdrawal (Preston et al. 1988; Mendelson et al. 1996, 1997, 1999; Fudala et al. 1998). Tablets containing buprenorphine and naloxone in a 4:1 ratio have been manufactured and are currently undergoing clinical testing.

While dissolving and injecting such tablets should be aversive for opioid-dependent people, the effects produced by buprenorphine/naloxone in opioid abusers who are not physically dependent are less clear. For example, it is possible the addition of naloxone to buprenorphine might attenuate the acute effects of buprenorphine. Indeed, one study comparing low doses of parenteral buprenorphine alone to buprenorphine combined with naloxone in non-dependent opioid abusers showed some attenuation of buprenorphine effects when naloxone was added (Weinhold et al. 1992).

While non-dependent opioid abusers may dissolve and inject tablets, it is also possible that such populations with less severe levels of opioid abuse will have lower rates of injecting drug use. These non-dependent abusers may experiment and abuse buprenorphine tablets via the sublingual route, if sufficient opioid agonist effects are produced. The purpose of this study was to examine the pharmacologic characteristics of sublingual buprenorphine/naloxone tablets in non-dependent opioid abusers, determining if buprenorphine effects are modulated by the addition of naloxone, and assessing the relative abuse potential of sublingual buprenorphine/naloxone tablets in this population.

Materials and methods

Subjects

Participants were seven adult volunteers with active opioid abuse, but not physically dependent. Pregnancy or significant medical or psychiatric illness (e.g., insulin-dependent diabetes, schizophrenia) were exclusionary. Individuals seeking substance abuse treatment were not enrolled but assisted in referral to community-based treatment programs.

All but one were male, average age was 38.4 years (range 33–47 years), average duration of illicit opioid use was 7 years (range 4–11 years), and number of illicit opioid uses per week was between 1 and 4. Participants underwent routine medical screening that included history and physical examination, EKG, and 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 problems. The study was approved by the Institutional Review Board; volunteers gave written informed consent and were paid for their participation.

Study setting

Subjects lived on a 14-bed behavioral 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 (Syva Co.). Breathalyzer testing for alcohol was done on the day of admission and at least twice weekly. No evidence of unauthorized drug or alcohol use during study participation was observed.

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 unit, consent was obtained, and they were introduced to the session room and the staff who would conduct the laboratory sessions. Participants were monitored drug-free for a minimum of 48 h after admission to the ward to ensure they had no evidence of physical dependence on opioids.

Each subject participated in a minimum of 13 experimental sessions (including a training session), and typically resided on the unit for 7 weeks. After completion of the inpatient portion of the study, subjects were discharged to an outpatient treatment/research clinic, and encouraged to participate in drug-free counseling services offered without charge.

Laboratory sessions

Subjects were informed they could receive combinations of buprenorphine and naloxone, as well as other opioid agonist medications or placebo. Examples of opioid agonists and antagonists and the types of effects produced by each were described to participants. No instructions regarding whether conditions would be repeated were given to subjects.

Sessions were conducted at the same time of day, twice weekly, with at least 72 h between sessions (i.e., either on Mondays and Thursdays or Tuesdays and Fridays). The session room, in a suite separate from the residential unit, contained two chairs, a Macin-

tosh 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. Fifteen minutes after the start of each session, 15 min of 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 received an intramuscular injection followed by the administration of sublingual tablets. The session then continued for 3 h, with data collected as described below.

A saline injection and placebo sublingual tablets were administered in the first session for each subject. This session followed the format of all subsequent sessions, including session staff being blind to the drug administered; it served as a training session, and was excluded from statistical analyses.

Physiological measures

Heart rate, blood pressure, skin temperature, respiratory rate, and oxygen saturation were monitored throughout the session. These measures were collected once per minute using a Criticare Non-Invasive Patient Monitor (model 507S, Criticare Systems, Inc., Waukesha, Mich., USA). 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 in 1-min intervals 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 camera with a ×2 magnification. Pupil photographs were taken three times 15 min before drug administration, and at 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, and 180 min after drug administration. The second pre-drug pupil photo was used for 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, 135, 150, 165 and 180 min after drug administration. Subjects were instructed to respond by describing how they felt at the time the questionnaire was being answered.

Subjects completed visual analog scales, a pharmacological class questionnaire, 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 labeled "None" and "Extremely", and responses were scored proportionately on a 100-point scale. The pharmacological class questionnaire asked the subject to select one of ten drug classes to which the administered drug was most similar: Placebo, Opioids, Opioid Antagonists, Phenothiazines, Barbiturates and Sleeping Medications, Antidepressants, Hallucinogens, Benzodiazepines, Stimulants, and Other. Examples for each drug class were listed on the questionnaire. The adjective rating questionnaire 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 a total score for each scale.

Observer ratings included the same adjective rating scale, as well as an assessment of seven signs of opioid withdrawal (lacrimation, rhinorrhea, perspiration, piloerection, bowel sounds, yawning, and restlessness). Each opioid withdrawal item was scored 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). Ratings were made by a research technician who was present throughout the session and blind to the drug administered. Observer ratings were done at the same times as the subject ratings. Item ratings were summed to produce total scores for the Agonist scale and Withdrawal scale.

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. 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 were completed during the baseline period (15 min before drug administration), and at the same times as (immediately following) the subject ratings.

Drugs and doses

All medications were administered using double-blind, double-dummy procedures. Eleven drug conditions were tested: placebo, hydromorphone 2 and 4 mg given by intramuscular injection, buprenorphine 4, 8, and 16 mg given as sublingual tablets, and buprenorphine/naloxone combinations 1/0.25, 2/0.5, 4/1, 8/2, and 16/4 mg given as sublingual tablets. A commercial preparation of hydromorphone hydrochloride (10 mg/ml; Knoll Pharmaceuticals, Whippany, N.J., USA) was diluted to the appropriate volume with bacteriostatic saline and used for the two hydromorphone dose conditions. Buprenorphine tablets were supplied by the National Institute on Drug Abuse, Research Technology Branch (Rockville, Md., USA) from a supply provided by Reckitt and Colman (Hull, UK). Tablets were in two sizes: small, which had a weight of100 mg, and large, which had a weight of 400 mg. Small tablets contained either placebo, or 2 mg of buprenorphine with 0.5 mg of naloxone. Large tablets 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.

Subjects received two and one-half 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 order of conditions for the sessions was derived from a Latin-square for 11 subjects. Subjects were assigned one of the schedules using a random number table.

The highest buprenorphine dose conditions (16 mg buprenorphine alone and 16 mg buprenorphine combined with 4 mg naloxone) were

each delivered as two large tablets. The two 8 mg dose conditions (8 mg buprenorphine alone and 8 mg buprenorphine combined with 2 mg naloxone) were each delivered as one large tablet. The 4 mg buprenorphine plus 1 mg naloxone condition was delivered as two small combination tablets, while the 4 mg dose of buprenorphine alone was delivered as one-half of one large tablet of buprenorphine alone. The 2 mg buprenorphine plus 0.5 mg naloxone condition was delivered as one small tablet, and the 1 mg buprenorphine plus 0.25 mg naloxone condition was delivered as one-half of one small tablet.

Data analysis

Peak values for each session were determined for each measure. For most measures this was an increased effect. However, since some measures decrease in response to acute opioid agonist effects in non-dependent subjects (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 saline 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 11 drug conditions and time (baseline versus peak effect). Differences between means that were greater than the Tukey HSD are reported as significant ($P<0.05$).

Time course effects were analyzed with a repeated measures analysis of variance. Main effects were the 11 drug conditions and 13 time points.

Results

Table 1 summarizes mean values and results of post hoc analyses comparing peak drug effect to peak placebo effect for subject, observer, physiologic, and psychomotor measures obtained during the experimental sessions.

Subjective effects

Mean peak visual analog scale ratings for measures which produced significant effects relative to placebo are presented in Fig. 1. Dose-related increases in ratings of Drug Effects, High, Good Effects, and Liking were seen for hydromorphone, for buprenorphine, and for the combination of buprenorphine/naloxone. The predominant effects were seen with the highest doses tested (hydromorphone 4 mg, buprenorphine/naloxone 8/2 and 16/4 mg, and buprenorphine 8 and 16 mg). None of the tested active drug conditions produced significant changes in ratings of Bad Effects or Sick.

For ratings of Drug Effects, only the two higher doses of buprenorphine alone (8 and 16 mg) produced significantly increased ratings compared to placebo ($q=5.56$, $df=22, 60$, $P<0.05$; $q=6.74$, $df=22, 60$, $P<0.01$, respectively). The combination dose of 8/2 mg produced ratings of drug effects that were lower (mean score=16.1; Table 1) than those produced by the buprenorphine dose of 8 mg (mean score=26.6). Similarly, the combination dose of 16/4 mg produced ratings of drug effects that were lower (mean score=25.0) than those produced by the buprenorphine dose of 16 mg (mean score=31.7). However, these differences between buprenorphine alone and the corresponding buprenorphine/naloxone doses were not statistically significant for these or any other measures.

This same pattern of ratings – lower scores for the combination dose when compared to the corresponding buprenorphine alone dose – was also seen for the other

Table 1 Summary of peak drug effects[a]

	Placebo	Intramuscular hydromorphone		Sublingual buprenorphine			Sublingual buprenorphine/naloxone				
		2	4	4	8	16	1/0.25	2/0.5	4/1	8/2	16/4
Subjective measures											
Visual analog scales											
High	1.6	10.1	23.1*	10.4	22.0*	29.4**	6.9	9.3	16.0	13.6	26.7**
Drug effects	2.4	9.4	23.3	11.9	26.6*	31.7**	12.0	9.9	17.1	16.1	25.0
Good effects	2.6	9.6	22.6	15.1	29.1*	33.4**	14.1	8.4	17.6	16.1	28.3
Liking	1.3	11.0	27.3	11.4	29.3*	32.0**	9.0	10.4	20.7	18.6	28.9*
Adjective agonist rating scale	11.9	11.3	13.7	12.0	13.3	16.0**	12.0	11.4	12.1	13.7	15.6*
Observer-rated measures											
Adjective agonist rating scale	11.7	13.1	16.3*	12.9	15.4	16.7**	14.0	12.4	14.3	17.9**	17.9**
Physiologic measures											
Skin temperature	81.4	91.0**	89.7*	90.0*	91.8**	91.8**	84.9	87.0	88.7	88.5	91.4**
Pupil diameter	4.3	3.0**	2.5**	2.9**	2.6**	2.4**	3.7	3.4**	3.1**	2.6**	2.4**
Oxygen saturation	97.9	97.6	97.3	97.5	97.1*	96.7**	97.4	97.7	97.7	97.4	97.0**
Psychomotor tasks											
Circular Lights	76.1	71.0	64.0	70.6	66.0	60.6**	70.7	71.9	67.0	54.7**	60.6**
Trails (total line length, cm)	542.0	601.1	609.8	698.4	685.5	677.9	596.3	558.6	581.3	665.7	836.4**

[a] Values shown are the mean peak response ($n=7$). All doses are in mg. Results shown are for items with a significant effect for at least one dose condition; comparisons are to peak placebo effect. For subjective measures, observer-rated measures, skin temperature, and the Trails outcome the maximum positive increase was examined. For all other physiological measures and Circular Lights the maximum decrease was examined

*$P<0.05$, **$P<0.01$

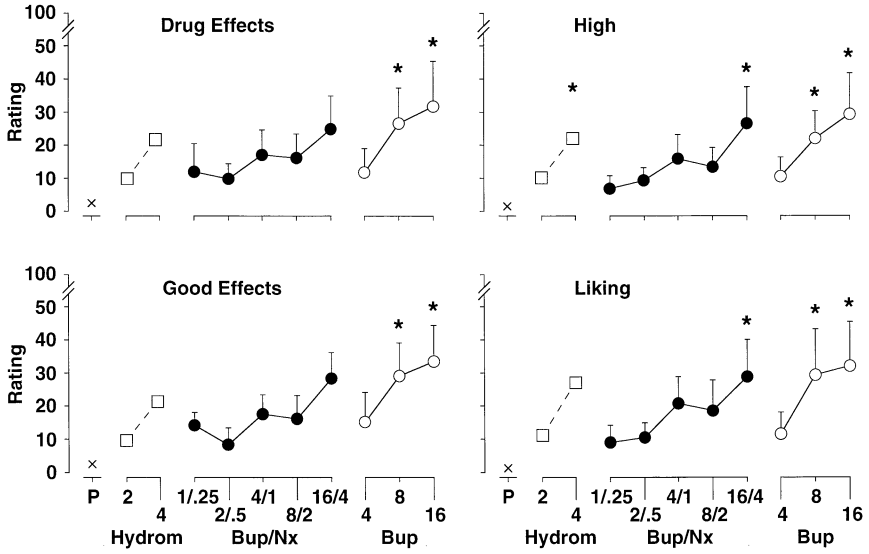

Fig. 1 Effects of acute intramuscular doses of hydromorphone, and acute sublingual doses of buprenorphine and buprenorphine/naloxone on subject-reported visual analog scale ratings in non-dependent opioid abusers. The maximum possible score was 100. Each *point* (and *bracket*) represents the mean peak value (±SE) for the seven subjects. *P* placebo, *Hydrom* hydromorphone, *Bup/Nx* buprenorphine/naloxone, *Bup* buprenorphine. All doses shown are in mg

visual analog scale measures typically associated with opioid agonist-like effects (High, Good Effects, Liking). For visual analog scale ratings of High, significantly increased ratings compared to placebo were seen for the higher dose of hydromorphone (q=5.69, df=22, 60, P<0.05), the highest dose of buprenorphine/naloxone (q=6.63, df=22, 60, P<0.01), and the 8 and 16 mg doses of buprenorphine alone (q=5.39, df=22, 60, P<0.05; q=7.35, df=22, 60, P<0.01, respectively). Mean ratings for the combination doses of 8/2 mg and 16/4 mg (13.6 and 26.7, respectively) were again lower than the comparable buprenorphine doses of 8 and 16 mg (22.0 and 29.4, respectively). Compared to placebo, ratings of Good Effects were significantly greater for the 8 and 16 mg doses of buprenorphine alone (q=5.43, df=22, 60, P<0.05; q=6.30, df=22, 60, P<0.01, respectively), while ratings of Liking were significantly greater for the 8 and 16 mg doses of buprenorphine alone (q=5.69, df=22, 60, P<0.05; q=6.24, df=22, 60, P<0.01, respectively), as well as the 16/4 mg combination dose alone (q=5.60, df=22, 60, P<0.05).

The lower test doses (hydromorphone 2 mg and buprenorphine/naloxone 1/.25 and 2/.5 mg) produced ratings that were generally modest and of similar magnitude. Interestingly, the buprenorphine/naloxone dose of 4/1 mg produced effects that were similar in magnitude to the combination dose of 8/2 mg for Drug Effects, High, Good Effects and Liking. In contrast, the buprenorphine dose of 4 mg produced ratings that were consistently lower than those seen for the 8 mg dose for these same four visual analog scale measures (Fig. 1).

Results from the subject adjective rating questionnaire showed only the highest doses of buprenorphine (16 mg) and buprenorphine/naloxone (16/4 mg) produced significantly increased ratings relative to placebo alone (q=6.43, df=22, 60, P<0.01; q=5.76, df=22, 60, P<0.05, respectively; Table 1). The results for the two conditions were quite similar; the mean rating on this measure for the 16 mg condition was 16.0, while the mean ratings for the 16/4 mg condition was 15.6. There were no significant results for the subject-rated adjective score for opioid withdrawal.

Participants' responses to the drug class identification questionnaire are presented in Table 2. Placebo was primarily identified as placebo (79%). The 2 mg dose of hydromorphone was identified as an opioid agonist 52% of the time, and placebo the remainder of the time, while the 4 mg dose was primarily identified as an opioid agonist (77% of identifications).

The 4 mg dose of buprenorphine was identified as placebo on nearly 50% of occasions, with all other identifications being as an opioid agonist. For the 8 and 16 mg doses of buprenorphine, the majority of identifications were as an opioid agonist. The frequency of ratings as an opioid agonist for these two doses of buprenorphine were similar to the rates of identification as an opioid agonist for the 4 mg dose of hydromorphone.

The drug identifications of buprenorphine/naloxone were more varied than for other conditions. The two lowest dose conditions, 1/0.25 and 2/0.5 mg, were primarily identified as placebo (60% and 55%, respectively). The 4/1 mg dose condition was identified as an opioid agonist (43%), placebo (39%), and other (18%), and these latter ratings were all in the non-specific class labeled other. The dose condition 8/2 mg was identified as an opioid agonist (63%), placebo (31%), other drug classes (5%), and an opioid antagonist (1%), while the 16/4 mg condition was identified as an opioid agonist nearly all the time (83%), with a few identifications as placebo (14%), and two identifications as cocaine (2%).

Observer-rated effects

When compared to placebo, higher doses of hydromorphone (q=6.05, df=22, 60, P<0.05), the 16 mg dose of buprenorphine alone (q=6.61, df=22, 60, P<0.01), and the two highest doses of buprenorphine/naloxone (8/2

Table 2 Drug identification responses[a]

Drug administered[b]	Opioid agonist	Placebo	Other classes[c]
Saline	14	66	4
Hydromorphone			
2	44	40	0
4	65	19	0
Buprenorphine			
4	43	41	0
8	62	19	3
16	63	21	0
Buprenorphine/naloxone			
1/0.25	29	50	5
2/0.5	38	46	0
4/1	36	33	15
8/2	53	26	5
16/4	70	12	2

[a] Numbers shown are the total number of drug identifications made for each dose condition administered. Total identifications for each dose condition = 84 (7 subjects×12 times each)
[b] Doses shown are in mg
[c] There were a total of 34 identifications for Other Classes, which represents the combined numbers of identifications as Others (28), Opioid Antagonists (2), Benzodiazepines (2), and Stimulants (2). There were no identifications as Antidepressants, Hallucinogens, Phenothiazines and Barbiturates

mg: q=8.13, df=22, 60, P<0.01; 16/4 mg: q=8.13, df=22, 60, P<0.01), produced significant peak scores on the adjective agonist scale completed by the trained observer (Table 1). The mean scores for both the 8/2 and 16/4 mg doses were 17.9, while the mean score for the 16 mg buprenorphine dose was 16.7, and that for the 4 mg hydromorphone dose was 16.3. None of the dose conditions tested produced significant effects on the observer's adjective scale score for opioid withdrawal, or the total Withdrawal Signs Score (Table 1).

Physiologic effects

None of the dose conditions tested produced significant changes on measures of blood pressure, heart rate, or respiratory rate. However, skin temperature was increased for both hydromorphone conditions (2 mg: q=6.31, df=22, 60, P<0.01; 4 mg: q=5.49, df=22, 60, P<0.05), all three of the buprenorphine conditions (4 mg: q=5.69, df=22, 60, P<0.05; 8 mg: q=6.84, df=22, 60, P<0.01; 16 mg: q=6.85, df=22, 60, P<0.01), and the highest dose of the buprenorphine/naloxone condition (q=6.59, df=22, 60, P<0.01). Similarly, pupil diameter showed significant constriction for all of the dose conditions tested except the lowest buprenorphine/naloxone condition (2 mg hydromorphone: q=8.82, df=22, 60, P<0.01; 4 mg hydromorphone: q=12.24, df=22, 60, P<0.01; 4 mg buprenorphine alone: q=9.37, df=22, 60, P<0.01; 8 mg buprenorphine alone: q=11.69, df=22, 60, P<0.01; 16 mg buprenorphine alone: q=12.99, df=22, 60, P<0.01; 2/0.5 mg buprenorphine/naloxone: q=6.16, df=22, 60, P<0.01; 4/1 mg buprenorphine/naloxone: q=8.07, df=22, 60, P<0.01; 8/2 mg buprenorphine/naloxone: q=11.35, df=22, 60, P<0.01; 16/4 mg buprenorphine/naloxone: q=12.72, df=22, 60, P<0.01). Finally, the physiologic measure oxygen saturation was decreased for the 8 and 16 mg buprenorphine dose conditions (q=5.53, df=22, 60, P<0.05; q=8.32, df=22, 60, P<0.01, respectively), and the 16/4 mg buprenorphine/naloxone dose condition (q=6.28, df=22, 60, P<0.01).

Psychomotor effects

Results from the DSST showed no significant changes for any of the dose conditions tested, and there were no significant differences for the total number of sequence errors made on the Trails task. However, the highest buprenorphine/naloxone dose (16/4 mg) produced a significantly higher total line length for the Trails when compared to placebo (q=7.06, df=22, 60, P<0.01; Table 1). The total line length when placebo was administered was 542 cm, compared to 836 cm for the 16/4 mg condition.

In addition, the circular lights task showed significant decreases in performance for the 16 mg buprenorphine dose (q=6.25, df=22, 60, P<0.01), and for the 8/2 and 16/4 mg buprenorphine/naloxone doses (q=8.61, df=22, 60, P<0.01; q=6.25, df=22, 60, P<0.01, respectively). This task tracks the number of correct responses in 60 s, and it has previously been shown to be sensitive to the acute effects of sedative-hypnotics (Griffiths et al. 1983). Results for the placebo condition showed subjects gave an average of 76 correct responses. For the 16 mg buprenorphine condition, this decreased to 61 responses, and for the 8/2 and 16/4 mg buprenorphine/naloxone conditions this decreased to 55 and 61 responses, respectively.

Time course effects

Results from analyses for time course effects are summarized in Table 3, and examples for five measures – subjects' visual analog scale ratings of Liking, observer adjective agonist scores, skin temperature, pupil diameter, and oxygen saturation – are shown in Fig. 2. Results presented in Fig. 2 are for placebo, the hydromorphone 4 mg control condition, and the three pairs of dose conditions in which buprenorphine was tested with versus without naloxone (i.e., 4 versus 4/1 mg, 8 versus 8/2 mg, and 16 versus 16/4 mg). These conditions were selected in order to illustrate any potential alteration of buprenorphine's effects by the addition of naloxone.

The Tukey Honestly Significant Difference (HSD) pairwise tests at individual time points found that on no occasion for any variable did the effects of buprenorphine/naloxone differ significantly from the effects of buprenorphine alone. Pairwise comparisons against pla-

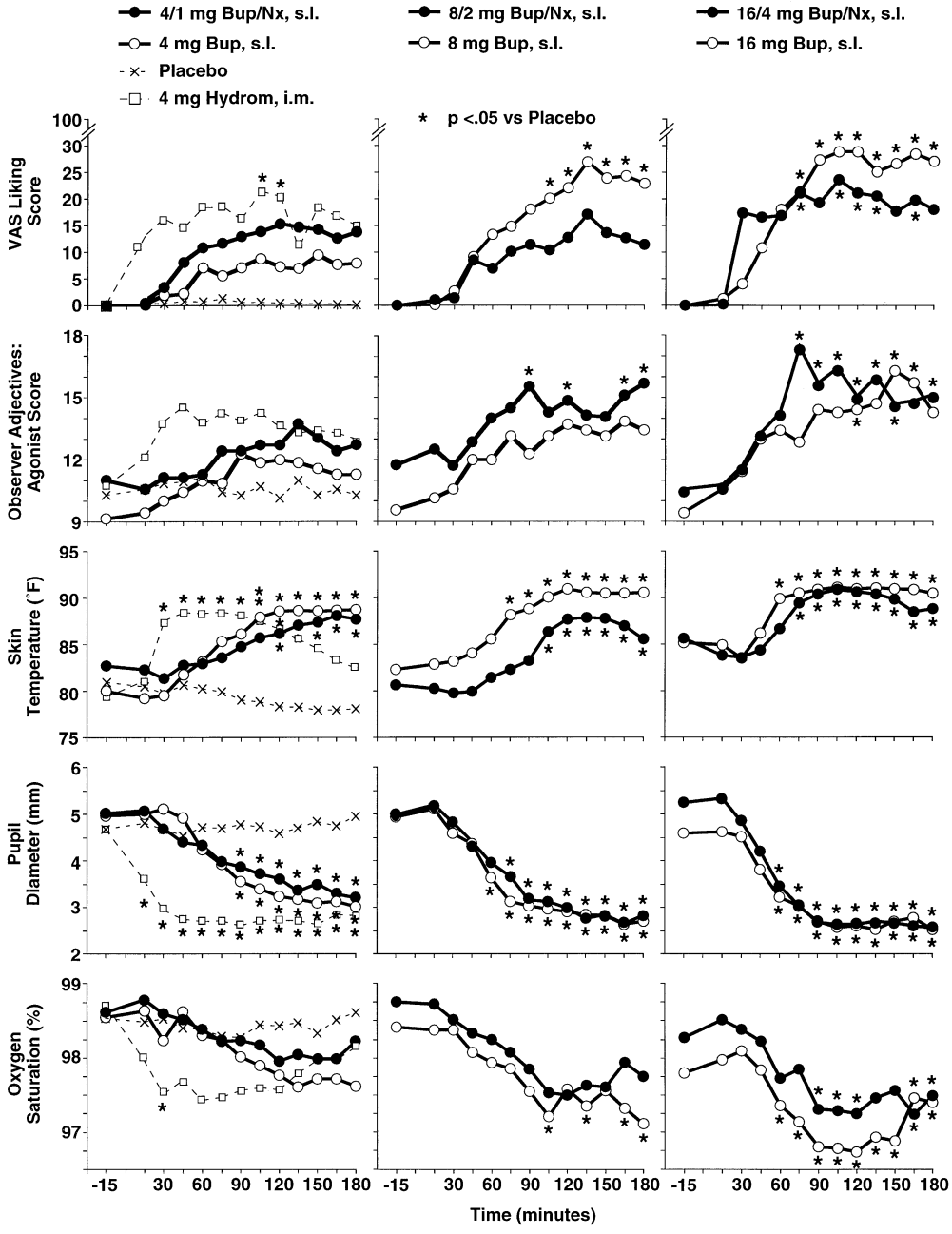

Fig. 2 Time course effects of placebo, intramuscular hydromorphone (4 mg) and sublingual doses of buprenorphine (4, 8, 16 mg) and buprenorphine/naloxone (4/1, 8/2, 16/4 mg) on measures of visual analog scale ratings of Liking, observer adjective agonist scores, skin temperature, pupil diameter, and oxygen saturation. Each *point* represents the mean based upon one observation in each of seven subjects. *Asterisks* indicate significant differences from placebo. There were no significant differences between buprenorphine alone and buprenorphine/naloxone. *Bup/Nx* buprenorphine/naloxone, *Bup* buprenorphine, *Hydrom* hydromorphone, *s.l.* sublingual, *i.m.* intramuscular, *VAS* visual analog scale

cebo revealed that buprenorphine/naloxone and buprenorphine alone had similar patterns of differing from placebo. Significant differences from placebo are indicated by asterisks in Fig. 2. Differences from placebo tended to reach statistical significance 60–90 min after drug administration.

For visual analog scale ratings of Liking and the observer's adjective agonist score (the top six panels in Fig.2), the relative magnitude of measures increased as a function of dose for both buprenorphine and buprenorphine/naloxone. While there were no significant differences between buprenorphine and buprenorphine/naloxone at any dose level, at some doses buprenorphine/naloxone appeared to produce lower ratings than buprenorphine alone (e.g., ratings of Liking for the 8 mg versus 8/2 mg doses). There were significant differences between active dose conditions and placebo at selected time points (shown by asterisks in Fig. 2). None of the buprenorphine or buprenorphine/naloxone conditions shown in Fig. 2 increased ratings until 30 min into the session, demonstrating the relatively slow onset of drug effects by the sublingual route (especially when compared to the parenteral administration of hydromorphone). However, analyses of time to peak effects showed no significant differences between the buprenorphine and buprenorphine/naloxone conditions compared to the hydromorphone control condition, for these two measures.

The three physiological measures shown in Fig. 2 (skin temperature, pupil diameter, oxygen saturation) showed clear changes over time, in a pattern consistent with acute

Table 3 Summary of time course analyses[a]

	F ratios			
	Condition (*df*=10, 60)	Time (*df*=12, 72)	C×T (*df*=120,720)	CD
Subjective measures				
Visual analog scales				
High	3.24**	5.53**	2.09	15.66
Drug effects	2.61	5.30**	2.00	17.45
Good effects	2.72	5.27**	1.81	19.25
Bad effects	0.97	1.12	1.00	17.25
Liking	2.58	4.93	1.92	19.36
Sick	0.98	1.02	0.97	14.54
Adjective rating scales				
Agonist	2.48**	4.56**	1.43	3.77
Withdrawal	1.49	1.44	0.83	2.45
Observer-rated measures				
Adjective rating scales				
Agonist	3.77**	9.69**	1.86**	4.19
Withdrawal	1.20	0.80	0.86	2.85
Withdrawal Signs Score	0.62	0.61	0.92	2.40
Physiologic measures				
Diastolic blood pressure	3.20**	1.05	1.17	9.56
Systolic blood pressure	1.82	0.96	1.37	12.98
Heart rate	0.81	64.18**	1.41	6.34
Respiration	1.32	2.46**	0.89	6.43
Skin temperature	3.06**	5.72**	3.69**	7.38
Pupil diameter	12.16**	202.02**	9.77**	0.80
Oxygen saturation	5.22**	15.41**	2.60**	0.79
Psychomotor tasks				
Circular Lights	3.30**	8.79**	1.80	12.15
Trails (total errors)	0.81	2.90**	1.03	5.74
Trails (total line length)	1.76	2.12	0.98	206.96
DSST (number correct)	3.98**	3.30**	1.44	11.28
DSST (% errors)	1.61	0.96	0.99	0.22

[a] Critical difference (CD) values shown are for $P<0.05$; $^{**}P<0.01$

opioid agonist effects in subjects not physically dependent upon opioids. That is, skin temperature increased, pupil diameter decreased, and oxygen saturation decreased. For most of the conditions and physiologic measures shown, there were no detectable differences between the buprenorphine and buprenorphine/naloxone conditions (although there were significant differences compared to placebo, again indicated by asterisks). Skin temperature did show a consistent but non-significant difference across time for the 8/2 mg versus 8 mg conditions, with less of an increase for the buprenorphine/naloxone condition. For skin temperature, it appears there was a delay in both onset of skin temperature increase by the buprenorphine/naloxone condition, and a failure to attain a similar peak effect.

Analyses of time to peak effects showed differences between hydromorphone and the buprenorphine and buprenorphine/naloxone conditions for pupil diameter and oxygen saturation (but not skin temperature). For pupil diameter, there was a significantly shorter time to peak effect for the hydromorphone condition compared to the 8 mg buprenorphine condition, and for oxygen saturation, there was a significantly shorter time to peak effect for the hydromorphone condition compared to all conditions shown except the 16 mg buprenorphine condition.

Discussion

This study examined the pharmacologic characteristics of sublingual buprenorphine and buprenorphine combined with naloxone delivered through a tablet formulation in volunteers with active opioid abuse but not physical dependence. In general, both buprenorphine alone and buprenorphine/naloxone produced a profile of effects similar to the opioid agonist control condition (hydromorphone), and no significant differences were found between comparable doses of buprenorphine and buprenorphine/naloxone. Thus, in this population of opioid abusers, buprenorphine/naloxone tablets appear to have abuse potential.

For some measures, such as visual analog scale ratings of High and observer adjective agonist scores, the peak responses for the 8 and 16 mg buprenorphine conditions, the 8/2 and 16/4 mg buprenorphine/naloxone conditions, and the 4 mg hydromorphone condition were similar (Table 1). Scores for these and other measures of opioid agonist effects were not markedly high (i.e., for a range of 0–100, the highest peak score for the visual analog scales was 33). Thus, buprenorphine and buprenorphine/naloxone tablets in the dose range tested have

moderate potential for abuse, comparable in magnitude to 4 mg of parenteral hydromorphone.

While the analysis of peak effects provides a useful summary of the outcomes from this study, it does not address how the onset of effects might influence abuse potential. An examination of time course effects shows that both buprenorphine and buprenorphine/naloxone had relatively slow onsets of effects in this study (Fig. 2). Fifteen minutes after receiving tablets, subjects were reporting essentially no Liking on a visual analog scale, and effects were still quite low at 30 min after drug administration for all conditions except the 16/4 mg dose. A similar pattern of effects was seen for observer-rated measures and physiologic measures (Fig. 2), further suggesting the abuse potential of tablets by the sublingual route should be moderate.

The purpose of adding naloxone to buprenorphine is to decrease abuse potential in opioid-dependent people who might inject buprenorphine. In abusers who are not physically dependent on opioids, the addition of naloxone will not exert a similar detrimental effect (i.e., precipitated withdrawal). However, there is some evidence to suggest that naloxone might attenuate the acute effects of buprenorphine (Weinhold et al. 1992). No significant differences between buprenorphine given alone and corresponding doses of buprenorphine combined with naloxone were seen in the present study. The 8 and 8/2 mg dose conditions suggested some attenuation of buprenorphine's effects due to the addition of naloxone (Fig. 2), especially as assessed by the visual analog scale ratings of Liking and skin temperature. However, these differences were small, non-significant, and not seen with other dose comparisons.

Three psychomotor tasks – Circular Lights, a form of the Trail-Making Test, and DSST – were completed by participants in this study. While the DSST showed no significant changes for any of the tested conditions, significant effects were found for Circular Lights and the Trail-Making Test (Table 1). The 16, 8/2, and 16/4 mg conditions each significantly decreased the number of correct responses for the Circular Lights task, similar to effects seen with acute doses of sedative-hypnotics and consistent with the expected sedating effects of acute doses of opioids in non-dependent subjects. For the Trails-Making Test, the total number of errors did not significantly change as a function of dose, but the total line length was significantly longer for the 16/4 mg condition. The total line length for the 16/4 mg condition was 836 cm, and was markedly greater than all other conditions tested. It is interesting to note that the corresponding dose of buprenorphine alone (16 mg) did not produce any marked change in total line length. Taken together, these results from performance tasks suggest acute doses of buprenorphine and buprenorphine combined with naloxone can produce mild impairments at high doses in this population.

This study tested the effects of buprenorphine and buprenorphine/naloxone only by the sublingual route and only in non-dependent volunteers. Tablets could be dissolved and injected, and if injected, the effects would be expected to have a more rapid onset. However, it is also possible that the greater bioavailability of naloxone by the parenteral route might result in an attenuation of buprenorphine effects. Study of parenteral buprenorphine and buprenorphine/naloxone in non-dependent opioid abusers would provide further useful data on the abuse potential of these products. Inclusion of these additional conditions in the present study was not practical.

The profile and magnitude of effects produced by buprenorphine and buprenorphine/naloxone, compared to parenteral hydromorphone, suggests that both medications may be abused by opioid users who are not physically dependent upon opioids. However, the slower onset of effects may make such tablets less desirable than a rapidly acting compound such as parenteral hydromorphone. Buprenorphine's other characteristics, such as its long duration of action, its safety at high doses, and its potentially mild withdrawal syndrome, are assets that make it an attractive medication for the treatment of opioid dependence. Thus, while buprenorphine and buprenorphine/naloxone tablets may be abused, this abuse potential may be lower than that seen with drugs typically injected, and the previously demonstrated beneficial features of buprenorphine and buprenorphine/naloxone support the continued development of this medication for the treatment of opioid dependence.

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