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ORIGINAL INVESTIGATION

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Buprenorphine sublingual tablets: effects on IV heroin self-administration by humans

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Abstract *Rationale:* Studies have shown that buprenorphine, a partial mu opioid agonist, effectively reduces heroin taking. While previous research with buprenorphine utilized a liquid formulation, a tablet formulation is proposed for clinical use. However, because recent research suggests that the liquid and tablet differ in bioavailability, it is unclear what dose of the buprenorphine tablet effectively antagonizes the reinforcing effects of heroin. *Objective:* The present study was designed to compare the effects of two sublingual doses of buprenorphine maintenance on heroin self-administration. *Methods:* Eight heroin-dependent men participated in a 6-week, double-blind, placebo-controlled inpatient study to evaluate the reinforcing effects of intravenous heroin (0, 6.25, 12.5, 25 mg) during maintenance on 8 or 16 mg sublingual buprenorphine. Participants first sampled the available dose of heroin, and then were allowed to respond under a progressive ratio schedule for either heroin or $20. For each heroin dose, one sample session and three choice sessions occurred. Two sessions per day were conducted. A sample session was followed by the first choice session on one day, and the second and third choice sessions occurred on the following day. These sessions were conducted while participants were maintained on daily doses of 8 or 16 mg buprenorphine (3 weeks each). *Results:* Relative to placebo, 12.5 and 25 mg heroin produced significant increases in break point values under both maintenance dose conditions. The mean break point value for 12.5 mg heroin was significantly lower under 16 mg buprenorphine, compared to 8 mg. *Conclusions:* These results demonstrate that the reinforcing effects of heroin were not fully antagonized by these doses of the tablet formulation of buprenorphine, and that 16 mg buprenorphine reduced heroin self-administration relative to 8 mg.

Keywords Buprenorphine · Heroin · Opioid · Progressive ratio · Self-administration · Subjective effect

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Introduction

The only federally approved medications for the treatment of opioid abuse are the full opioid agonists, methadone and levo-α-acetylmethadol, and the opioid antagonist, naltrexone. Buprenorphine, a partial agonist at the mu subtype and an antagonist at the kappa subtype of opioid receptor (Cowan et al. 1977a, b; Lewis 1985; Martin et al. 1976), has many features that make it useful for treating heroin dependence. Buprenorphine produces some agonist effects, thus promoting patient compliance. However, it also blocks the intense euphoric effects of full agonists (Bickel et al. 1988b; Jasinski et al. 1978; Rosen et al. 1994; Schuh et al. 1999; Walsh et al. 1995b). For example, Bickel et al. (1988b) showed that maintenance on 8 and 16 mg sublingual buprenorphine liquid significantly attenuated the subjective effects of hydromorphone (up to 18 mg subcutaneously). Because many of buprenorphine's effects are less-than-maximal over a wide dose range, it has a large margin of safety and low potential for overdose (Bickel and Amass 1995; Walsh et al. 1994, 1995a, b). For example, buprenorphine produces dose-related decreases in respiratory rate up to a certain dose, but further increases in dose do not produce further decreases in respiratory rate (see, for example, Walsh et al. 1994). Furthermore, buprenorphine has high affinity for mu receptors and has been characterized as “irreversible” because it dissociates very slowly from opioid receptors. This characteristic of buprenorphine may underlie its long duration of action, which makes less-than-daily dosing with buprenorphine feasible (Amass et al. 1994; Bickel et al. 1999; Fudala et al. 1990; Petry et al. 1999). Buprenorphine's long duration of action, as well as its partial agonist effects, may con-

tribute to its mild withdrawal effects upon discontinuation of treatment (Dum et al. 1981; Heel et al. 1979; Jasinski et al. 1978; Kosten and Kleber 1988; Kosten et al. 1990, 1991; Mello and Mendelson 1980; Mello et al. 1981; Woods and Gmerek 1985).

Results from both phase I and phase II testing with buprenorphine in humans have indicated that it is a safe, effective treatment medication for opioid dependence (Bickel et al. 1988a; Bigelow and Preston 1992; Johnson and Fudala 1992; Johnson et al. 1995; for review, see Bickel and Amass 1995). Several studies showed that approximately 8 mg sublingual buprenorphine was as effective as 50–60 mg oral methadone in treating opioid abuse, as measured by retention in treatment and drug toxicology results from observed urine samples (Johnson et al. 1992; Strain et al. 1994; however, see Ling et al. 1996). In addition to the clinical studies, buprenorphine effectively reduced opioid self-administration by humans (Mello and Mendelson 1980; Mello et al. 1982) and nonhumans (see, for example, Mello et al. 1983; Winger et al. 1992) in laboratory studies. For example, Mello and colleagues showed that maintenance on 8 mg subcutaneous buprenorphine reduced intravenous heroin self-administration by 69% to 98% (Mello and Mendelson 1980; Mello et al. 1982). Participants in that study resided on an inpatient ward and responded under an operant schedule for either money or heroin (up to 40.5 mg/day in three divided doses of 13.5 mg/dose). In contrast, Greenwald and colleagues (1999) showed that the sublingual liquid formulation of buprenorphine (2, 4, and 8 mg) did not significantly reduce the reinforcing effects of intramuscular hydromorphone, using a multiple choice procedure (Griffiths et al. 1996) in an outpatient treatment study. The inconsistency between the studies by Mello and colleagues, and Greenwald and colleagues was likely due to a number of procedural differences (different routes of buprenorphine administration, inpatient versus outpatient research settings, different methods of evaluating reinforcing effects, etc.).

Although virtually all of the studies described above utilized a liquid formulation of buprenorphine, it is expected that a tablet formulation will be used clinically. However, recent studies have suggested that the bioavailability of the tablet formulation is approximately 50% that of the liquid formulation (Nath et al. 1999; Schuh and Johanson 1999). The purpose of the present study was to evaluate the reinforcing effects of intravenous heroin under maintenance on 8 and 16 mg of the sublingual buprenorphine tablets. A placebo maintenance condition was not tested in the current study because it would have been necessary to completely detoxify participants from heroin dependence, which would have increased the study duration and dropout rate. The hypothesis of the study was that the reinforcing and subjective effects of heroin would be reduced under 16 mg buprenorphine, relative to 8 mg.

Materials and methods

Participants

Fourteen heroin-dependent individuals (nine non-Hispanic Caucasian males, four Hispanic males, and one African American female), who currently were not seeking treatment for their drug use, began the 6-week protocol. Eight male (six non-Hispanic Caucasian, two Hispanic) healthy volunteers aged 30 to 38 years (mean: 33.6 years) completed the study. Volunteers who completed the study reported using heroin for an average of 10.9 years (range: 5–19 years). All participants were currently dependent on heroin, and reported spending an average of $55 per day (range: $25 to $90) on heroin. Seven participants smoked tobacco cigarettes (10–20 cigarettes per day), six participants used cocaine (two times per week or less), two participants used alcohol (three times per week or less), and two participants used marijuana (once per month).

After an initial telephone interview, eligible participants received additional screening at the laboratory, which included completing detailed questionnaires on drug use, general health, and medical history, and a medical and psychological evaluation. Participants were told that they might be maintained on an opioid for the duration of the study, and that different doses of the maintenance medication might be tested. An electrocardiogram and Mantoux test or chest X-ray were also performed. Routine laboratory analyses included a blood chemistry panel, thyroid function test, syphilis screening, and urinalysis. Urine drug toxicologies (opioids, cocaine, benzodiazepines, cannabinoids, and amphetamines) were also performed using a radiative energy attenuation and fluorescence polarization immunoassay system (AD_x System; Abbott Laboratories, Abbott Park, Ill., USA).

Participants were excluded from the study if they were pregnant or nursing, seeking drug treatment, dependent on illicit drugs other than opioids, or had a major axis I psychiatric diagnosis other than opioid dependence. Those who had recent histories of violence or who were on parole/probation were excluded from the study. Participants were required to be physically healthy, and fully able to perform all study procedures. They were dependent on opioids, as verified by a naloxone challenge test (Wang 1974), and reported having had experience using heroin by the intravenous route.

Prior to admission, participants completed a training session, during which the study procedures were explained to them in detail. Volunteers were paid $25 per inpatient day and an additional $25 per day bonus if they completed the study. In addition, they could receive up to $40 per day during the experimental sessions. Participants signed consent forms describing the aims of the study, and the potential risks and benefits of participation. Participants were offered free HIV testing, and drug and risk reduction education, and were offered referrals for treatment. This study was approved by the Institutional Review Board of the New York State Psychiatric Institute.

Apparatus

During experimental sessions, participants were seated in a room equipped with Macintosh computers. All computer activities, vital signs, and behaviors were continuously monitored by the experimenters in an adjacent control room via a continuous on-line computer network, video cameras, and vital signs monitors (cardiovascular function was measured using a Sentry II Vital Signs Monitor; NBS Medical, Costa Mesa, Calif., USA, arterial oxygen saturation was measured using a pulse oximeter Model 400; Palco Laboratories, Santa Cruz, Calif., USA). Communication between the staff and participants was kept to a minimum during experimental sessions.

General procedures

The reinforcing effects of intravenous heroin (placebo, 6.25, 12.5, and 25 mg) were evaluated under two sublingual buprenorphine

maintenance dose conditions (8 and 16 mg). All participants received both doses of buprenorphine: half of the participants received 8 mg first, and half of the participants received 16 mg first. They received each dose for 3 weeks (weeks 1–3 and weeks 4–6). During weeks 1 and 4, participants were stabilized on the appropriate dose of buprenorphine. Testing occurred during weeks 2, 3, 5, and 6 on Monday, Tuesday, Thursday, and Friday morning and afternoon. Heroin doses were administered in non-systematic order both within and between participants, except that the highest heroin dose was never tested first. On Monday and Thursday morning, participants received $20 and a bolus sample dose of heroin. During the next three choice sessions, participants could work to receive all, or part of the sampled heroin dose or money amount. The first choice session occurred during the afternoon following the sample session, and the second and third choice sessions occurred on the following day in the morning and afternoon. The total amount of heroin and/or money chosen during the self-administration task was given as a bolus dose at the end of the task. An interdose interval of 5 h was used for heroin administration; this interdose interval was used because it mimics the typical pattern of heroin use reported by heroin-dependent individuals.

Experimental sessions

During all sessions, participants completed computerized tasks and subjective-effects questionnaires. Heart rate and blood pressure were measured every 2 min, and blood oxygen saturation was monitored continuously with a pulse oximeter and recorded every minute during experimental sessions. Pupil photographs were taken repeatedly during the sessions. Participants received breakfast between 0800 and 0900 hours and lunch between 1230 and 1330 hours. Experimental sessions occurred between 0900 and 1100 hours and 1400 and 1600 hours. Participants were not allowed to smoke tobacco cigarettes during experimental sessions.

Sample session

Physiologic, subjective, and performance effects were measured both before and after drug administration (see descriptions below). Heroin or placebo was administered only if vital signs were within safe limits (SpO_2>93%). A photograph was taken of the right pupil before (–45 and 0 min) and 4, 10, 20, 40, and 60 min after drug administration. The subjective-effects battery (see description below) was administered before and 4, 40, and 60 min after drug administration. The performance battery (see description below) was administered before and 10 min after drug administration. The Subjective Opioid Withdrawal Scale (SOWS) was administered before and 65 min after drug administration. The Drug Effects Questionnaire (DEQ) was administered 60 min after drug administration.

Choice sessions

Choice sessions were similar in design to the sample session, except that participants completed a self-administration task (see below) after the first performance battery. Participants were instructed to choose between $20 and the dose of heroin that they received during the sample session. A pupil photograph was taken before (–65, –30, and 0 min) heroin administration. The subjective-effects battery (see description below) was administered before, and 4 and 40 min after drug administration. Choice sessions were otherwise identical to the sample session.

Self-administration task

Participants were told that they could work for all or part of the sampled dose of heroin or the sampled money amount ($20) by choosing the drug or money option each time a choice was available. Responses consisted of finger presses on a computer mouse. Standardized instructions were read to each participant explaining the self-administration task. Heroin and money were available under independent progressive ratio schedules, and participants were given ten opportunities to choose between the two options. Ten percent of that day's heroin dose or money value was available at each choice opportunity. Thus, if the dose of heroin for that day was 25 mg, at each opportunity participants could respond for 2.5 mg (10% of 25 mg) or $2 (10% of $20). Completion of the ratio requirement for each choice was accompanied by a visual stimulus on the computer screen. The response requirement for each of the two options increased independently such that the initial ratio requirement for each option was 50 responses; the ratio increased progressively each time the option was selected (50, 100, 200, 400, 800, 1,200, 1,600, 2,000, 2,400, 2,800). In order to receive all of the heroin or money available that day, participants were required to emit 11,550 responses within 40 min. Fewer total responses were required if choices were distributed between the two options. These ratio values were chosen based on previous research conducted in our laboratory (Comer et al. 1997, 1998, 1999). Although it required sustained, high rates of responding, participants were capable of completing 11,550 responses in the allotted time.

At the start of each self-administration task, two illustrations appeared on the computer screen: an empty balance scale and an empty bank. As each choice was completed, either the scale was implemented with a pile of powder or a dollar sign was added to the bank. Thus, participants could always see how many money and drug choices had been made. At the end of the 40-min self-administration task, the participant received whatever he had chosen: money and/or drug.

Subjective measures

Four questionnaires were used to assess subjective effects. The first questionnaire was a 26-item visual analog scale (VAS) designed to assess subjective and physiological effects (modified from Foltin and Fischman 1995). The first 18 lines were labeled with adjectives describing mood states (for example, “I feel...:” “high”) and 4 additional lines were labeled with questions about the dose just received (i.e., “I liked the dose,” “For this dose, I would pay”). Participants also indicated, by making a mark along a 100-mm line, how much they “wanted” each of the following drugs: heroin, cocaine, alcohol, and tobacco. Participants rated each item on the VAS from “Not at all” (0 mm) to “Extremely” (100 mm), except for the “For this dose, I would pay” question, which ranged between $0 (0 mm) to $20 (100 mm). The second questionnaire was a 13-item opioid symptom checklist consisting of true/false questions designed to measure opioid effects (for example, “My skin is itchy,” etc.; Foltin and Fischman 1992; Fraser et al. 1961). The VAS and opioid symptom checklist together constituted the subjective-effects battery. The third questionnaire was the 16-item SOWS (Handelsman et al. 1987). Participants rated each item on a scale from 0 to 4, with 0 being “Not at all” and 4 being “Extremely” (for example, “I have gooseflesh,” etc.). The fourth questionnaire was a 6-item DEQ (Evans et al. 1995). Participants described drug effects by selecting among a series of possible answers ranging from 0 (“No effects at all”) to 4 [“Very strong (good, bad, etc.) effects”]. Ratings of drug liking ranged between –4 (“Dislike very much”) to 4 (“Like very much”).

Task battery

The task battery consisted of four tasks: a 3-min digit-symbol substitution task (McLeod et al. 1982), a 10-min divided attention task (Miller et al. 1988), a 10-min rapid information processing task (Wesnes and Warburton 1983), and a 3-min repeated acquisition of response sequences task (Kelly et al. 1993).

Physiological measures

A blood pressure cuff was attached to the non-dominant arm, and blood pressure was recorded automatically every 2 min. Participants were also connected to a pulse oximeter via a soft sensor on a finger of the non-dominant hand, which monitored arterial blood oxygen saturation (%SpO_2). For safety, supplemental oxygen (2 l/min) was provided via a nasal cannula during all experimental sessions. A specially modified Polaroid camera with a close-up lens (2× magnification) was used to take pupil photographs. All photographs were taken under ambient lighting conditions. Horizontal and vertical measurements of pupil diameter were made using calipers, and then these two measurements were averaged and divided by 2 to correct for the 2× magnification.

Drugs

Heroin HCl was provided by the National Institutes on Drug Abuse (Rockville, Md., USA) and prepared by the Columbia-Presbyterian Medical Center research pharmacy. A 25 mg/ml heroin concentration was prepared in a 5% dextrose solution to enhance stability. Dose calculations were based on the hydrochloride salt form. Heroin was stored in a freezer and used within 3 months of preparation. The stock solution was diluted in 5% dextrose to produce each dose. Placebo (5% dextrose solution) or heroin (6.25, 12.5, and 25 mg) was administered intravenously over a 30-s period in a total volume of 2 ml. Physiological saline solution was infused continuously during experimental sessions, except during drug administration. Between 1 and 2 ml heparinized saline (10 units/ml) was flushed into the catheter four to eight times each day. All venous catheters were maintained as heplocks and were removed within 60 h of insertion.

Buprenorphine HCl tablets (8 mg per active tablet, 0 mg per placebo tablet) were provided by the National Institutes on Drug Abuse. Buprenorphine dosing occurred at 8 p.m. each evening, and was supervised by a nurse. Participants were instructed to hold the tablets under the tongue for 10 min, without swallowing. Compliance was verified midway through the dosing period by a mouth check. Upon admission to the hospital, participants were inducted directly onto either 8 or 16 mg buprenorphine (i.e., the dose was not incrementally increased). Blood samples were collected each morning prior to experimental sessions, corresponding to approximately 13–14 h post-buprenorphine administration.

Plasma levels of buprenorphine and norbuprenorphine were measured using an HP 5988B mass spectrometer. Internal standards buprenorphine-d_3 (25 ng) and buprenorphine-d_4 (25 ng) were added to a plasma sample (1.0 ml) containing 100 µl 5% NaF, followed by deproteinization with 5% sulfosalicylic acid and centrifugation. One milliliter of 1 M carbonate buffer (pH 10.5) and 5 ml $CHCl_3$/2-propanol/heptane (25:10:65) were added to the supernatant. The mixture was then centrifuged and evaporated to dryness. The residue was derivatized with 50 µl TFAA in 100 µl chloroform, dried down in a vacuum centrifuge, redissolved in 40 µl 1% TFAA in butyl chloride, and then transferred to a sample vial for GC-MS measurement. Determination of plasma samples was calculated based on the peak-area using the isotope dilution method. Linear curves were obtained over concentration ranges of approximately 1–100 ng/ml (r^2=0.998) for buprenorphine and approximately 0.5–100 ng/ml (r^2=0.999) for norbuprenorphine. The detectable limits for buprenorphine and norbuprenorphine were 1.0 and 0.5 ng/ml, respectively. The doses of heroin and buprenorphine were administered in a double-blind fashion.

Supplemental medications available to all participants for the duration of the study included Mylanta, acetaminophen, ibuprofen, Colace, Milk of Magnesia, and multivitamins with iron. Trazodone (50 mg p.o., at bedtime; Warner Chilcott, Morris Plains, N.J., USA) was available if participants reported having trouble sleeping.

Morning urine samples were collected daily and one random sample per week was screened for the presence of other illicit substances. No illicit substances were found in the participants' urine samples.

Statistical analyses

Repeated measures analyses of variance (ANOVAs) were performed for progressive ratio break point values (the highest ratio that participants completed). The analyses were designed to answer four basic questions:

1. Does each heroin dose function as a reinforcer under each buprenorphine maintenance condition?
2. Do the reinforcing effects of heroin differ under 8 versus 16 mg buprenorphine?
3. Do the reinforcing effects of heroin vary across choice sessions?
4. Is heroin a more efficacious reinforcer than money?

Heroin and money break point values, and response rate were analyzed as a function of buprenorphine dose (8, 16 mg), heroin dose (placebo, 6.25, 12.5, and 25 mg intravenously), and choice session (first, second, or third).

The following planned comparisons were performed to answer the first three questions above: (1) each active heroin dose was compared to placebo, (2) break point values for each heroin dose were compared under 8 and 16 mg buprenorphine, and (3) break point values during each of the three choice sessions were compared under each buprenorphine and heroin dose. To answer the fourth question, two post hoc comparisons were performed for break point values for heroin and for money (i.e., under each buprenorphine maintenance dose, the peak break point values for heroin and money were compared).

Repeated measures ANOVAs were also performed for pupil diameter, task performance, VAS and DEQ ratings, opioid symptom checklist ratings, and SOWS ratings during the sample session. Data were analyzed as a function of buprenorphine dose and heroin dose, collapsing across time. Pulse oximeter data obtained during the morning sample session were averaged within participants, and analyzed as a function of buprenorphine dose and heroin dose. Planned comparisons were similar to those described above (questions 1 and 2). To evaluate potential carry-over effects after 25 mg heroin, one post hoc comparison was performed: the pre-heroin baseline time point during the morning sample session was compared to the baseline time point during the afternoon choice session for the VAS and opioid symptom checklist.

SOWS data during the buprenorphine stabilization weeks (1 and 4) were also analyzed using repeated measures ANOVAs. SOWS data were first analyzed between groups (half of the participants received 8 mg buprenorphine first, and half received 16 mg buprenorphine first). There were no significant differences between groups, so the data were pooled and analyzed as a function of stabilization week and day. To determine whether there were any differences in withdrawal on the day prior to testing, a post hoc comparison was made for that day between week 1 and week 4. Although heart rate and blood pressure were measured during experimental sessions, the data were not analyzed because a large number of data points were lost due to equipment malfunction on several days for several participants. Plasma levels of buprenorphine and norbuprenorphine were analyzed as a function of buprenorphine maintenance dose. Results were considered statistically significant at P<0.05, using Hunyh-Feldt corrections, where appropriate.

Results

Choice

Figure 1 shows mean progressive ratio break point values for heroin (left panel) and money (right panel) as a function of heroin dose and buprenorphine maintenance dose. Mean heroin break point values for both 12.5 [8 mg: $F(1,21)$=21.8, P<0.0003; 16 mg: $F(1,21)$=9.8, P<0.007] and 25 mg [8 mg: $F(1,21)$=28.4, P<0.0001;

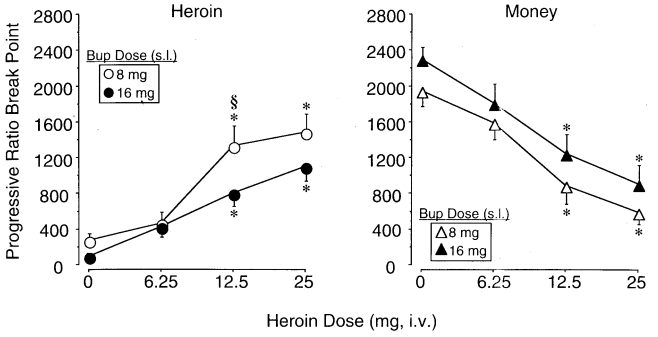

Fig. 1 Progressive ratio break point values for heroin (*left panel*) and money (*right panel*) as a function of heroin dose and buprenorphine (*Bup*) maintenance dose. Break point values could range between 0 and 2,800. Data points represent the mean across eight participants and three choice sessions (24 observations per data point). *Error bars* represent ±1 SEM. * Indicates significant differences from placebo, § indicates significant differences between 8 and 16 mg buprenorphine. *s.l.* Sublingual

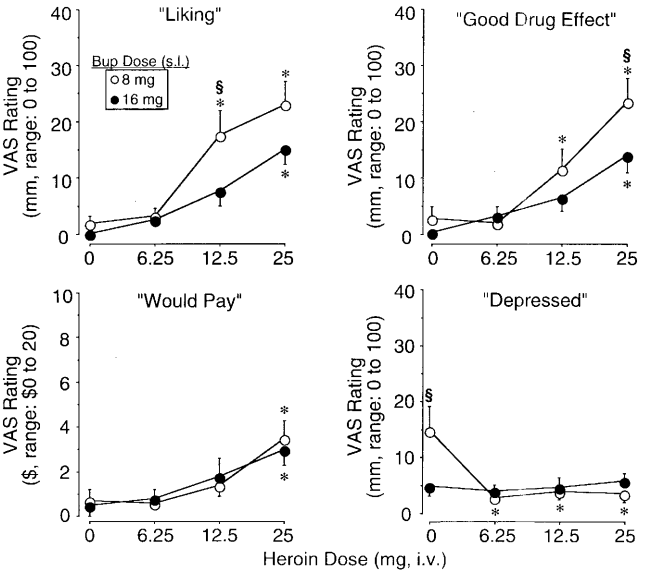

Fig. 2 Selected visual analog scale (VAS) ratings during the sample session as a function of heroin dose and buprenorphine dose. The VAS rating scale ranged between 0 and 100 mm. Ratings of the amount of money participants would pay for the dose sampled ranged between $0 and $20. Data points represent mean ratings across time for the eight participants. *Error bars* represent ±1 SEM. * Indicates significant differences from placebo, § indicates significant differences between 8 and 16 mg buprenorphine

16 mg: $F(1,21)=19.6$, $P<0.0004$] heroin were significantly greater than placebo under each maintenance condition. Maximal heroin break point values occurred at 25 mg heroin under both buprenorphine maintenance doses (1,483 and 1,100 responses under 8 and 16 mg buprenorphine, respectively). Break point values for 25 mg heroin were 26% lower under 16 mg buprenorphine, relative to 8 mg. Comparing across maintenance doses, break point values were significantly lower after 12.5 mg heroin under 16 mg buprenorphine [40% decrease; $F(1,21)=5.4$, $P<0.03$]. There were no statistically significant differences in heroin break point values across the three choice sessions at any dose tested, suggesting that any potential carry-over effects from the morning to the afternoon sessions did not significantly alter the reinforcing effects of heroin.

Mean money break point values for both 12.5 [8 mg: $F(1,21)=15.1$, $P<0.001$; 16 mg: $F(1,21)=14.8$, $P<0.001$] and 25 mg [8 mg: $F(1,21)=24.9$, $P<0.0001$; 16 mg: $F(1,21)=25.9$, $P<0.0001$] heroin were significantly lower than placebo under each maintenance condition (Fig. 1 right panel). Maximal money break point values occurred at placebo under both buprenorphine maintenance doses (1,950 and 2,300 responses under 8 and 16 mg buprenorphine, respectively). There were no statistically significant differences in break point values for money across the three choice opportunities. In addition, there were no significant differences in money break point values as a function of buprenorphine maintenance dose.

Under 16 mg buprenorphine, the maximal heroin break point value (25 mg) was significantly lower than the maximal money break point value [placebo; $F(1,21)=11.9$, $P<0.003$]. Under 8 mg buprenorphine, the maximal heroin break point value (25 mg) did not significantly differ from the maximal money break point value.

There were no significant changes in response rate as a function of heroin dose or buprenorphine dose.

Subjective effects

Figure 2 shows selected mean VAS ratings collected during the sample session as a function of heroin dose and buprenorphine maintenance dose. There were four patterns of responding on the VAS, as illustrated in Fig. 2. Ratings of drug "Liking" (upper left panel) and "Stimulated" (data not shown) had a pattern similar to the choice data: heroin produced dose-related increases in subjective ratings, with the greatest difference between 8 and 16 mg buprenorphine occurring at the 12.5 mg heroin dose ["Liking": $F(1,21)=5.4$, $P<0.03$; "Stimulated": $F(1,21)=4.7$, $P<0.05$]. Ratings of "Good Drug Effect" (upper right panel), "High," and "Sedated," (data not shown) had a pattern in which heroin produced dose-related increases in subjective ratings, with the greatest difference between 8 and 16 mg buprenorphine occurring at the 25 mg heroin dose ["Good Drug Effect": $F(1,21)=5.0$, $P<0.04$; "High": $F(1,21)=7.9$, $P<0.01$; "Sedated": $F(1,21)=5.3$, $P<0.03$]. Ratings of the amount of money participants would pay for heroin (lower left panel), the quality of heroin, the potency of heroin, and ratings of "Mellow" (data not shown) had a pattern in which heroin produced dose-related increases in subjective ratings, but there were no significant differences in ratings between the two buprenorphine maintenance doses. Ratings of "Depressed" (lower right panel) and "Anxious" (data not shown) were elevated after placebo administration under the 8 mg buprenorphine maintenance dose condition relative to 16 mg buprenorphine ["Depressed": $F(1,21)=6.0$, $P<0.05$; "Anxious": $F(1,21)=$

5.9, $P<0.05$]. Ratings of wanting heroin and tobacco were consistently elevated (mean ratings were between 60 and 70 mm), and ratings of wanting alcohol and cocaine were near-zero across heroin and buprenorphine doses (data not shown). VAS ratings of "High," drug "Liking," and amount participants would be willing to pay for drug after 25 mg heroin under 8 mg buprenorphine maintenance were significantly elevated during the afternoon choice session baseline, relative to the morning sample session baseline ["High": $F(1,84)=6.1$, $P<0.03$; "Liking": $F(1,84)=4.8$, $P<0.04$; amount would pay: $F(1,84)=9.2$, $P<0.02$].

The pattern of results obtained from the opioid symptom checklist were somewhat similar to the VAS. Ratings of "High" were similar to the choice data and VAS ratings of drug "Liking" (Fig. 2 upper left panel) in that heroin produced dose-related increases in subjective ratings, with the greatest difference between the 8 and 16 mg buprenorphine maintenance dose occurring at the 12.5 mg heroin dose [$F(1,21)=7.8$, $P<0.02$]. Ratings of "Nodding," "Relaxed," and "Skin Itchy," were only significantly different from placebo after 25 mg heroin under 8 mg buprenorphine maintenance ["Nodding" $F(1,21)=11.8$, $P<0.003$; "Relaxed" $F(1,21)=5.6$, $P<0.04$; "Skin Itchy" $F(1,21)=35.5$, $P<0.0001$]; active heroin doses were not significantly different from placebo under 16 mg buprenorphine. The only effect that showed a significant difference between 8 and 16 mg buprenorphine was "Skin Itchy" at the 25 mg heroin dose [$F(1,21)=20.0$, $P<0.0004$], when participants reported having more itchy skin under 8 mg buprenorphine. Opioid symptom checklist ratings of "High," "Nodding," and "Pleasant Sick" after 25 mg heroin under 8 mg buprenorphine maintenance were significantly elevated during the afternoon choice session baseline, relative to the morning sample session baseline ["High" $F(1,21)=15.5$, $P<0.001$; "Nodding" $F(1,21)=11.1$, $P<0.01$; "Pleasant Sick" $F(1,21)=6.0$, $P<0.04$].

Heroin produced dose-related increases in DEQ ratings of "Good Drug Effect," drug liking, desire to take the drug again, and strength of drug effect under both buprenorphine maintenance doses. Comparing across the 8 and 16 mg buprenorphine maintenance doses, ratings of "Good Drug Effect," drug "Liking," strength of drug effect, and type of drug after 25 mg heroin were significantly elevated under 8 mg buprenorphine, relative to 25 mg heroin under 16 mg buprenorphine ["Good Drug Effect" $F(1,21)=14.4$, $P<0.001$; "Liking" $F(1,21)=9.5$, $P<0.006$; strength of drug effect $F(1,21)=11.3$, $P<0.003$; type of drug $F(1,21)=8.4$, $P<0.01$].

Subjective ratings of opioid withdrawal, as measured by total scores on the SOWS (maximum score =64), were significantly elevated during the first stabilization week (13.9±1.6), compared to the second stabilization week [5.7±0.6; data not shown; $F(1,7)=10.5$, $P<0.01$]. During admission day, after receiving their first dose of buprenorphine, all but one participant reported withdrawal (SOWS scores ranged between 0 and 24, out of a maximum possible score of 64). There was little evidence of buprenorphine-precipitated withdrawal on the day of admission because buprenorphine was administered at 8 p.m., several hours after participants last used heroin. During the peak of withdrawal (the 3rd day after induction onto buprenorphine), SOWS scores ranged between 7 and 46. Seven of the participants requested clonazepam (for sedation) during the first stabilization week, five of the participants requested ketorolac tromethamine (for muscle pain), one participant requested compazine (for nausea), and three participants requested clonidine (for general withdrawal symptoms). Although withdrawal peaked on the 3rd day during the first stabilization week (19.0±4.9), scores on the day prior to testing during the first and second stabilization periods were not different. During testing, total SOWS scores after placebo administration under 8 mg buprenorphine were significantly elevated, relative to 25 mg heroin [data not shown; $F(1,21)=9.6$, $P<0.01$]. Individual items that contributed to this effect were increased ratings of "Anxious," "Bones Ache," "Restless," and "Yawning."

Performance tasks

There were few effects of heroin on performance, with the exception that the number of false alarms on the rapid information processing task significantly increased (from 86 to 105) after administration of 25 mg heroin, relative to placebo, under 16 mg buprenorphine [$F(1,21)=4.7$, $P<0.04$]. Performance on the divided attention task was significantly impaired by 16 mg buprenorphine relative to 8 mg buprenorphine: the speed with which participants tracked a moving stimulus was lower under 16 mg buprenorphine [placebo: $F(1,21)=5.0$, $P<0.04$; 6.25 mg heroin: $F(1,21)=6.2$, $P<0.02$, corresponding to a 1.1 and 1.2 pixel/s difference between 8 and 16 mg buprenorphine], and the distance between the moving stimulus and the cursor was greater after 6.25 mg [$F(1,21)=6.4$, $P<0.02$] and 25 mg heroin [$F(1,21)=7.9$, $P<0.01$], corresponding to a 9,223- and 10,219-pixel difference between 8 and 16 mg buprenorphine.

Physiological effects

Under 8 mg buprenorphine, heroin produced dose-related decreases in pupil diameter [data not shown; 25 mg heroin: $F(1,21)=11.7$, $P<0.003$]. Pupil diameter also decreased with increasing heroin dose under 16 mg buprenorphine, but this change was not statistically significant. There were no significant differences in pupil diameter between 8 and 16 mg buprenorphine. The average arterial oxygen saturation throughout the sample session did not change across heroin doses (data not shown). Comparing across 8 and 16 mg buprenorphine, arterial oxygen saturation was lower under 16 mg buprenorphine, but only significantly so after 25 mg heroin [$F(1,21)=4.8$, $P<0.04$]. These changes in oxygen satura-

tion occurred in the presence of supplemental oxygen, and were not clinically significant.

Plasma drug levels

Mean plasma levels of norbuprenorphine were 1.3 (±0.1) and 2.2 (±0.1) ng/ml approximately 14 h after administration of 8 and 16 mg buprenorphine, respectively. This difference in plasma level was statistically significant [$F(1,7)=8.5$, $P<0.02$]. Norbuprenorphine plasma levels ranged between 0.4 and 2.4 ng/ml during 8 mg buprenorphine maintenance, and 0.8 and 3.6 ng/ml during 16 mg buprenorphine maintenance. Plasma levels of buprenorphine were generally lower than the limit of detectability of the assay system used. Only one of eight participants tested showed measurable plasma levels of buprenorphine (peak: 4.5 ng/ml after 16 mg buprenorphine).

Discussion

These data demonstrate that heroin self-administration under 16 mg of the tablet formulation of buprenorphine was reduced relative to 8 mg buprenorphine. These results differ from those reported in a previous study evaluating the effects of maintenance on the liquid formulation of buprenorphine (Greenwald et al. 1999). In that study, buprenorphine (2, 4, and 8 mg) did not produce dose-related antagonism of the reinforcing effects of intramuscular hydromorphone. The 4 and 8 mg doses of liquid buprenorphine were approximately bioequivalent with the 8 and 16 mg tablet doses used in the present study. One possible reason for this difference in results is that the study by Greenwald et al. (1999) was conducted on an outpatient basis, which can be problematic in that illicit drug use may obscure the effects of the experimental manipulation. In addition, the tasks used to measure the reinforcing effects of hydromorphone/heroin were not comparable in that Greenwald et al. (1999) used a procedure in which there was a long delay between choice and drug administration, the opioids being tested were different, and the opioids were administered via different routes (intravenous versus intramuscular).

The only other laboratory study evaluating opioid self-administration under buprenorphine maintenance was conducted by Mello and colleagues (Mello and Mendelson 1980; Mello et al. 1982), who showed that intravenous heroin self-administration was almost completely blocked by 8 mg subcutaneous buprenorphine, relative to placebo. In the current study, heroin self-administration was only partially reduced by 16 mg sublingual buprenorphine, relative to 8 mg sublingual buprenorphine. This difference between the study by Mello and colleagues and the current study is likely due to important procedural differences. For example, buprenorphine was administered by different routes (sublingual in the present study compared to subcutaneous in the study by Mello and colleagues). As reported by Jasinski et al. (1989), the relative potency of sublingual to subcutaneous buprenorphine for physiological and behavioral effects in men with histories of opioid abuse was approximately two-thirds. Given the further difference in bioavailability between the liquid and tablet formulations of buprenorphine, a dose of approximately 24 mg of the tablet formulation would have been equivalent to 8 mg subcutaneously administered buprenorphine.

A second reason for the difference between the results reported here and those reported by Mello and colleagues may be that the maximal heroin doses tested were different (25 mg heroin in the present study compared to 13.5 mg in the study by Mello and colleagues). Larger doses were tested in the present study to reflect the higher purity levels of heroin available today: participants in our previous studies under morphine maintenance generally reported that the 25 mg heroin dose produced effects comparable to one to two street bags of heroin, which is the amount typically used during each "shot" on the street. In the present study, self-administration of 12.5 mg heroin was significantly reduced by 16 mg buprenorphine, relative to 8 mg buprenorphine. While these data suggest that buprenorphine produced a downward shift in the heroin dose-response curve, it was not possible to determine whether buprenorphine also produced a rightward shift in the heroin dose-response curve. Although 25 mg heroin appears to have surmounted the blockade produced by 16 mg buprenorphine, it is not clear whether doses larger than 25 mg heroin would have produced further increases in break point values.

In the present study, the reinforcing effects of money decreased with increasing heroin doses, which is consistent with our previous studies (Comer et al. 1997, 1998). One interesting finding in the present study is that under 16 mg buprenorphine, the maximal ratio completed for money was significantly greater than the maximal ratio completed for heroin, suggesting that money was a more effective reinforcer than the doses of heroin tested under 16 mg buprenorphine. In our previous study of intravenous heroin versus $10, $20, or $40 under morphine maintenance (Comer et al. 1998), the maximal ratio for heroin was always higher than that for money. The data in the present study thus suggest that 16 mg buprenorphine reduced the reinforcing efficacy of heroin. In contrast, heroin and money were equally efficacious reinforcers under 8 mg buprenorphine.

The subjective-effects data collected during the sample session in the present study were generally consistent with the choice data, and with previous reports of buprenorphine's effects on opioid agonists (Bickel et al. 1988b; Rosen et al. 1994; Schuh et al. 1999). Namely, ratings of heroin "Liking," "Good Drug Effect," and "High" were significantly lower under 16 mg buprenorphine, relative to 8 mg buprenorphine. In contrast, ratings of the amount of money participants would pay for the dose sampled, as well as the "Potency" and "Quality" of heroin were not significantly different under the two maintenance dose conditions. Therefore, the latter subjective effects do not appear to predict heroin self-ad-

ministration. This variability in subjective effects has been shown in previous studies. Bickel and colleagues (1988b) showed that equivalent doses of the liquid formulation of buprenorphine (4 and 8 mg) did not uniformly produce dose-related blockade of hydromorphone's subjective effects. For example, 8 mg buprenorphine produced greater blockade than 4 mg buprenorphine on an opioid agonist adjective rating scale and a drug effect analog scale, but ratings of "High" did not appear to differ under 4 and 8 mg buprenorphine. In the present study, ratings of "I feel..." "Depressed" and "Anxious," as well as total scores on the SOWS were significantly elevated after placebo administration under the 8 mg buprenorphine maintenance dose condition, indicating that participants were experiencing mild withdrawal. In two previous studies conducted in our laboratory, withdrawal was not reported after placebo administration under morphine maintenance conditions (Comer et al. 1998, 1999). However, some individual items on the SOWS ("Yawning" and "Restless") were significantly elevated after placebo administration in another study of intranasal heroin under morphine maintenance (Comer et al. 1997). Again, the reason for this variability in effect is unclear.

After administration of various doses of heroin, performance on the rapid information processing and divided attention tasks was impaired under 16 mg buprenorphine, relative to 8 mg. Previous studies of acute administration of buprenorphine generally have reported that buprenorphine impairs psychomotor performance (Macdonald et al. 1989; O'Neill 1994; Zacny et al. 1997; but see Walsh et al. 1994). For example, Zacny et al. (1997) showed that performance of the Digit Symbol Substitution task, as well as four other psychomotor tests, was impaired in a dose-related manner after acute, intravenous administration of buprenorphine. However, Mello et al. (1982) reported that during maintenance on buprenorphine, performance of an operant task (button presses on a manipulandum) was not impaired, relative to a placebo-maintained group. In the present study, the degree of impairment produced by 16 mg buprenorphine in combination with heroin was relatively small.

The physiological effects of buprenorphine were also consistent with previous studies. After placebo administration, pupil diameter under 8 and 16 mg buprenorphine was not significantly different in the present study. Walsh et al. (1994) also reported no significant differences in pupil diameter after equivalent doses of buprenorphine (4 and 8 mg sublingual liquid). Furthermore, in the present study, 16 mg buprenorphine completely antagonized the miotic effects of up to 25 mg heroin, which is also consistent with Walsh and colleagues (1995b), who showed that an equivalent dose of buprenorphine antagonized up to 4 mg intramuscular hydromorphone. However, Bickel et al. (1988b) showed that pupils were significantly constricted after 18 mg hydromorphone in combination with 8 mg sublingual liquid buprenorphine. In the present study, oxygen saturation was generally not affected by buprenorphine, except that it was significantly lower after 25 mg heroin under 16 mg buprenorphine. These data are not surprising, given that participants received supplemental oxygen during all experimental sessions. In a previous study in our laboratory (Comer et al. 1999), doses up to 25 mg intravenous heroin did not significantly reduce arterial oxygen saturation in morphine-maintained participants, who were also receiving supplemental oxygen.

Plasma levels of buprenorphine were generally not measurable in the present study (the limit of detectability of our assay was approximately 1 ng/ml). This result was not entirely unexpected because samples were collected approximately 14 h after drug administration. Nath et al. (1999), as well as Schuh and Johanson (1999), reported that plasma concentrations of buprenorphine were less than 1 ng/ml by 12–24 h after administration of 8 mg buprenorphine tablet. Peak plasma concentrations of buprenorphine (2.9 ng/ml) occurred 1–2 h after administration of the 8-mg tablet (Nath et al. 1999; Schuh and Johanson 1999). There are currently no published reports of the pharmacokinetics of 16 mg of the tablet formulation of buprenorphine. However, Walsh et al. (1994) showed that 8 mg buprenorphine liquid (which is approximately bioequivalent with 16 mg buprenorphine tablet) produced mean plasma concentrations of approximately 1.5 ng/ml 12 h after drug administration. Therefore, given the limit of detectability of our assay, the results reported here were not entirely surprising.

In conclusion, results of the present study demonstrate that 16 mg of the tablet formulation of buprenorphine significantly decreased intravenous heroin self-administration, relative to 8 mg buprenorphine. However, the present data suggest that larger doses of the buprenorphine tablet (24 or 32 mg) should be evaluated to determine whether they are more effective in blocking the reinforcing effects of heroin.

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