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Effects of an alternative reinforcer on intravenous heroin self-administration by humans

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Abstract

Five heroin-dependent research volunteers, maintained on divided daily oral morphine doses, participated in an inpatient study designed to evaluate intravenous (i.v.) heroin self-administration when money ($10, $20 or $40) was concurrently available. Each morning participants received a single injection of heroin (placebo, 6.25, 12.5, 25, or 50 mg/70 kg, i.v.) and each afternoon, they had the opportunity to self-administer all or part of the morning dose. Participants responded under a progressive-ratio schedule (50, 100, ..., 2800) during a 10-trial self-administration task. During each trial, participants could respond for 1/10th of the sampled heroin dose or 1/10th of a single money value. The progressive-ratio value increased independently for each option. The total amount of heroin and/or money chosen during the self-administration task was administered at the end of the task. Heroin dose-dependently increased ratings of 'good drug effect' and 'high', impaired task performance and decreased pupil diameter and blood oxygen saturation. Heroin also dose-dependently increased progressive-ratio break point values, which varied as a function of the alternative money amount. Consistent with previous studies, the present results demonstrate that alternative reinforcers, depending on magnitude, are effective in reducing heroin use in opioid-dependent individuals. © 1998 Elsevier Science B.V.

Keywords: Heroin; (Human); Opioid; Performance; Progressive ratio; Self-administration; Subjective effect

1. Introduction

Currently, there are only three federally-approved medications for the treatment of opioid abuse: methadone (Kreek, 1973; Martin et al., 1973a; Kleber et al., 1980), levo-α-acetylmethadol (Jaffe et al., 1970; Senay et al., 1977; Freedman and Czertko, 1981) and naltrexone (Martin et al., 1973b; O'Brien, 1976; Mendelson and Mello, 1978; Meyer and Mirin, 1979; Judson et al., 1981). Although all of these medications have demonstrated efficacy in reducing heroin use, each is associated with certain problems. The primary purpose of the present study was to develop a heroin self-administration procedure that will allow a rapid evaluation of new treatment medications for opioid abuse. We will use this procedure to examine the conditions under which pharmacological, behavioral and combined pharmacological and behavioral interventions will reduce heroin self-administration. In previous models of heroin self-administration by humans, individuals typically had relatively unlimited access to heroin throughout the day, with constraints on maximal dose and on interdose interval (Altman et al., 1976; Mendelson and Mello, 1978; Meyer and Mirin, 1979; Mello and Mendelson, 1980). Although these studies allowed the measurement of the patterning of heroin self-administration throughout the day, it was difficult to test a wide range of heroin doses because of time considerations. Studies of methadone self-administration by humans have tested a wider range of doses (Stitzer et al., 1983; Spiga et al., 1996), but dose-ranging studies with heroin have not been conducted in humans. A major strength of the current procedure is that the reinforcing, subjective and physiological effects of a range of heroin doses can be tested in the same individual.

In the present study, the self-administration of heroin (placebo, 6.25, 12.5, 25 and 50 mg/70 kg) was evaluated in oral morphine-maintained individuals when money ($10,

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$20 or $40) was concurrently available. In this procedure, participants could choose between heroin and money under a modified progressive-ratio schedule. A choice procedure was used because it more closely models street heroin use, in which individuals may choose among a range of reinforcers (e.g. heroin, money, food). Ultimately, the objective was to determine a money value that would engender the most lawful heroin dose–response function (i.e. dose-related increases in responding for heroin). A money value that is too low presumably will be ineffective in competing with heroin and participants will choose heroin almost exclusively, regardless of dose. Conversely, if a money value is too high, participants may predominantly choose money. The hypothesis was that heroin self-administration would increase in a dose-related manner under all alternative money conditions but that the heroin progressive-ratio break point (i.e. highest ratio value completed) would decrease as the value of the monetary alternative increased. A progressive-ratio procedure was used in the present study because it allows a direct comparison of heroin's relative reinforcing strength at different doses under different money conditions. Progressive ratio schedules, which generate lawful dose–response functions, have been used extensively in laboratory animals (for review, see Johanson and Schuster, 1981) because, unlike other self-administration procedures, the primary dependent measure (break point) is minimally affected by direct rate-suppressing effects produced by the drug itself. Physiological effects (heart rate, systolic, diastolic and mean arterial pressure, arterial oxygen saturation and pupil diameter) were measured repeatedly during experimental sessions. In addition, subjective effects and psychomotor task performance were assessed both before and after heroin administration.

Our ultimate goal is to evaluate the efficacy of treatment medications for heroin dependence. Therefore, it was important to develop this self-administration procedure in heroin-dependent individuals. However, in order to control for opioid withdrawal, all participants were maintained on oral morphine. We chose oral morphine because (1) it prevents physical withdrawal, (2) it has little or no positive reinforcing effects of its own after chronic administration, perhaps due to the formation of normetabolites (Fraser et al., 1978a,b; Bertalmio et al., 1992) and (3) the time-course of morphine and heroin are very similar (Reisine and Pasternak, 1996), which made it possible to maintain individuals on a dosing schedule that mimics patterns of street heroin use.

2. Materials and methods

2.1. Participants

One African American and four non-Hispanic Caucasian healthy male volunteers aged 24 to 45 years (mean $\pm$ standard deviation (S.D.): 35 ± 8) participated. Intravenous heroin was the drug of choice for all five individuals, who reported between 2.5 and 25 years of heroin use (mean $\pm$ S.D.: 11.3 ± 4.3). All participants were currently dependent on heroin and they reported spending between $30 and $75 per day on heroin (mean $\pm$ S.D.: $49 $\pm$ $17). None was currently seeking treatment for his drug use, although all had previously been treated for heroin dependence. Four participants smoked tobacco cigarettes (range: 10 to 30 cigarettes per day); four participants reported current alcohol use (range: one to seven times per week); two participants reported current barbiturate use (range: one to two times per week); one participant reported current marijuana use (range: one to two times per week) and three participants reported current cocaine use (range: once a week or less). All five participants were unemployed prior to participation in the current study.

Initially, volunteers completed a telephone interview designed to assess personal, drug use, legal and medical histories. Eighty-two potential participants were interviewed by telephone. Of those, 26 received additional screening at the laboratory which included detailed personal history, general health and medical history questionnaires, a survey of eating habits and a medical and psychological evaluation. An electrocardiogram and Mantoux test or chest X-ray were also performed. Routine laboratory analyses included a blood chemistry panel, thyroid function tests, syphilis serology 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, IL).

Participants were excluded from the study if they were seeking drug treatment, dependent on illicit drugs other than opioids and/or had major affective, psychotic, or anxiety disorders. Participants who had a recent history of violence or who were on parole/probation were also excluded from the study. In order to participate in the study, participants were required to be physically healthy and fully able to perform all study procedures. Participants had to be both physiologically dependent on heroin and experienced with the intravenous route of heroin administration. Dependence was verified by a naloxone challenge test (Wang et al., 1974).

Prior to admission, participants received a tour of the facilities and a training session, during which the study procedures were explained to them in detail. Participants were paid for their time and participation in the screening and training sessions ($15 per screening visit and $25 per training session). Individuals who participated in the study protocols were paid $35 per day and an additional $35 per day bonus upon completion of the study. In addition, participants could receive between $10 and $40 per day during the experimental sessions. Participants signed consent forms describing the aims of the study, the screening

process and the known potential risks and benefits of participating in the study. This study was approved by the Institutional Review Board of the New York State Psychiatric Institute.

2.2. Apparatus

Participants were admitted to the New York State Psychiatric Institute for a period of 24 or 25 days. They resided on the General Clinical Research Service and participated in experimental sessions at the Substance Use Research Center. On Monday through Friday, participants engaged in two sessions per day, each session lasting between 2 and 2.5 h. During experimental sessions, participants were seated in private rooms equipped with a Macintosh LCIII computer with a keyboard and a mouse controller, on which participants completed all questionnaires and tasks. 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 (heart rate, systolic pressure, diastolic pressure and mean arterial pressure were measured using a Sentry II Vital Signs Monitor, NBS Medical, Costa Mesa, CA; arterial oxygen saturation was measured using a pulse oximeter Model 400, Palco Laboratories, Santa Cruz, CA). Communication between the staff and participants was kept to a minimum during experimental sessions.

2.3. General procedures

During a morning session, participants sampled heroin or placebo and during an afternoon session, participants had the opportunity to choose between the dose they sampled in the morning and the designated money value for that day. For each participant, three money values were tested in combination with a range of heroin doses. Each money value was held constant over consecutive days until the entire heroin dose range was tested. A new money value was then made available and the entire range of heroin doses was again tested. Heroin doses and money values were administered in nonsystematic order both within and between participants, except that the highest heroin dose was never tested first. Throughout the study, participants were maintained on oral morphine to prevent withdrawal (see description in Section 2.4).

2.4. Experimental sessions

During all sessions, participants completed computerized tasks and subjective-effects questionnaires. Heart rate, systolic pressure, diastolic pressure and mean arterial pressure were measured every 2 min with an NBS monitor and arterial oxygen saturation was monitored continuously with a pulse oximeter and recorded every minute during experimental sessions. In addition, blood samples were collected and pupil photographs were taken repeatedly during the sessions. At the beginning and end of every session, opioid withdrawal symptoms were assessed using the subjective opioid withdrawal scale and the objective opioid withdrawal scale (see Section 2.6). Participants were not allowed to smoke during experimental sessions.

2.4.1. Morning sample session

Physiologic, subjective and performance effects were measured both before and after drug administration (see detailed descriptions below). Heroin or placebo was administered only if vital signs were within safe limits (arterial oxygen saturation $> 92\%$). Blood samples were taken before and 2, 4, 10, 20, 40 and 60 min after drug administration. A photograph was taken of the right pupil before and 4, 40 and 60 min after drug administration. The subjective-effects battery (see detailed description below) was completed before and 4, 40 and 60 min after drug administration. The performance battery (see detailed description in Section 2.7) was completed before and 10 min after drug administration. The subjective and objective withdrawal questionnaires were completed before and 60 min after drug administration. After vital signs monitoring was discontinued, participants were taken to a waiting area, given their morphine supplement and escorted back to the General Clinical Research Service.

2.4.2. Afternoon self-administration session

The afternoon self-administration session was similar in design to the sample session, except that participants completed a self-administration task (see Section 2.5) after the first performance battery. Immediately prior to the self-administration task, participants were informed of the money amount available that day and they were told that they could choose between that money amount and the dose of heroin that they received during the morning sample session. A pupil photograph was taken before and 4, 40 and 60 min after heroin administration. All other aspects of the self-administration session were identical to the morning sample session.

2.5. Self-administration task

Participants were told that they could work for all or part of the dose of drug sampled that morning or the amount of money available that day by responding on the manipulandum (pressing on the computer mouse) each time a choice was available. Heroin and money were available under independent progressive ratio schedules and participants were given 10 opportunities to choose between the two options. 10% 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 50 mg/70 kg and the amount of money was $10, at each opportunity participants would be able to respond for 5 mg/70 kg

(10% of 50 mg) or $1 (10% of $10). 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 and increased progressively each time the option was selected (50, 100, 200, 400, 800, 1200, 1600, 2000, 2400, 2800). In order to receive all of the heroin or money available that day, subjects were required to emit 11,550 responses within 40 min. Fewer responses were required if choices were distributed between the two options.

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. Participants could thus always see how many money and drug choices had been made. At the end of the 40-min self-administration task, a research nurse gave the participant whatever he chose: money and/or drug. Heroin was thus administered as a bolus injection twice each day: once during the morning sample session and once at the end of the afternoon self-administration task.

2.6. Subjective and objective measures

Three questionnaires were used to assess subjective effects throughout the two experimental sessions. The first questionnaire was a 50-item visual analog scale designed to assess subjective and physiological effects (modified from Foltin and Fischman, 1995). Participants indicated along a 100 mm horizontal line the degree to which they were experiencing a particular effect (i.e. stimulated, anxious, depressed, sedated, high, hungry, friendly, miserable, on edge, alert, tired, talkative, self-confident, social, irritable, confused, a good drug effect, a bad drug effect, dizzy, sleepy, energetic, jittery, content, unmotivated, restless, nauseated, mellow, suicidal, forgetful, clumsy, withdrawn, heaviness in my limbs, upset stomach, blurred vision, difficulty concentrating, muscle pain, yawning, runny nose, headache, flu-like symptoms, sweating, trouble sleeping, chills, dreaming more, vomiting, gooseflesh, stomach pain, heart pounding or beating faster than usual, numbness or tingling in my extremities, noises or sounds seem louder than usual). The second questionnaire was a 13-item opioid symptom checklist consisting of true/false questions designed to measure opioid effects (i.e. normal, itchy skin, relaxed, coasting, nodding, high, sleepy, drunken, nervous, drive, 'on a soapbox' (need to talk), stomach turning, pleasant sick (Fraser et al., 1961; Martin and Fraser, 1961; Foltin and Fischman, 1992)). A score of 1 indicated that a symptom was present and a score of 0 indicated that it was absent. Total scores consisted of summing 'true' scores for each symptom, except the 'normal' item. When that item was 'true', one was subtracted from the total score. The visual analog scale and opioid symptom checklist together constituted the subjective-effects battery. The third questionnaire was the 16-item subjective opioid withdrawal symptom questionnaire (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' (i.e. anxious, yawning, perspiring, eyes tearing, nose running, gooseflesh, shaking, hot flashes, cold flashes, bones and muscles ache, restless, nauseated, vomiting, muscles twitch, stomach cramps and feel like shooting up now). The research nurse was trained to use the 13-item objective opioid withdrawal symptom questionnaire, which measured observable withdrawal symptoms (i.e. yawning, rhinorrhea, piloerection, perspiration, lacrimation, mydriasis, tremors, hot and cold flashes, restlessness, vomiting, muscle twitches, abdominal cramps and anxiety (Handelsman et al., 1987)). A score of 1 indicated that a symptom was present and a score of 0 indicated that it was absent. Total scores were the sum of all scores for each symptom.

2.7. Task battery

The performance task battery consisted of four tasks: the first task was a 3-min digit-symbol substitution task, which consisted of nine numbered random 3-row by 3-column squares (with one square blackened per row) displayed across the top of the computer screen (McLeod et al., 1982). A randomly generated number indicated which of the nine patterns should be emulated on a keypad by the subject on a particular trial. Participants were required to emulate as many patterns as possible by entering the patterns associated with randomly generated numbers appearing on the bottom of the screen. The second task was a 10 min divided attention task, which consisted of a concurrent pursuit-tracking task and a vigilance task (Miller et al., 1988). Participants tracked a moving stimulus on the video screen using the mouse and also signaled when a small black square appeared at any of the four corners of the video screen. The third task was a 10 min rapid information processing task, during which a series of digits was displayed rapidly on the computer screen (100 digits/min) and subjects were instructed to press a key as quickly as possible after three consecutive odd or even digits (Wesnes and Warburton, 1983). The fourth task was a 3-min repeated acquisition of response sequences task, during which four buttons were illuminated, and subjects were instructed to learn a 10-response sequence of button presses (Kelly et al., 1993). A position counter incremented by one each time a correct button was pressed and remained unchanged whenever the participant responded on an incorrect button. A points counter increased by one each time the 10-response sequence was correctly completed. The sequence remained the same throughout the 3 min task, but a new, random sequence was generated every time the task occurred again. Participants were instructed to earn as many points as possible during the 3 min task by pressing the buttons in the correct sequence.

2.8. Physiological measures

A blood pressure cuff was attached to the non-dominant arm (the left arm in all individuals), which recorded automated readings every 2 min. Participants were also connected to a pulse oximeter via a soft sensor on a finger on the non-dominant hand, which monitored arterial oxygen saturation. Transient, but substantial decreases in blood oxygen saturation occurred in the first three participants tested with 50 mg/70 kg heroin. Therefore, for safety, supplemental oxygen (2 l/min) was provided to the last two participants 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 a calipers and then these two measurements were averaged and then divided by 2 to correct for the 2 × magnification.

2.9. Drugs

Heroin HCl, suitable for human use, was provided by the National Institutes on Drug Abuse (Rockville, MD) and prepared by the Columbia-Presbyterian Medical Center research pharmacy. A 50 mg/ml heroin concentration was prepared in a 5% dextrose solution to enhance stability. Dose calculations were based on the salt form. Heroin was stored in a refrigerator and used within 2 weeks of preparation. The stock solution was diluted in saline to achieve each dose. A research nurse administered 2 ml of placebo (physiological saline, 0.9%) or heroin (6.25, 12.5, 25 and 50 mg/70 kg) intravenously to participants over a 30 s period. Heroin or placebo was administered at approximately 1000 and 1500 during experimental sessions. This 5 h interdose interval was chosen based on interviews with heroin-dependent individuals, who typically reported a 4–8 h interdose interval. Two venous catheters were in place: one for drug administration and another for collection of blood samples. For drug administration, a 20-gauge catheter was inserted into the dominant forearm and for blood collection, an 18-gauge catheter was inserted into the non-dominant forearm (Angiocath, Becton Dickenson, Sandy, UT). Physiological saline was infused continuously, except during actual drug administration, into the drug administration catheter during experimental sessions. Between 1 and 2 ml heparin (10 units/ml) was flushed into each catheter four to eight times each day. All venous catheters were maintained as heplocks and were removed within 60 h of insertion.

Supplemental medications available to all participants for the duration of the study included: Mylanta®, acetaminophen, ibuprofen, Colace®, Milk of Magnesia® and multi-vitamins with iron. Clonidine HCl (0.3 mg; Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT), ketorolac tromethamine (30 mg; Roche Laboratories, Nutley, NJ) and oxazepam (30 mg; Wyeth-Ayerst Laboratories, Philadelphia, PA) were available for the first three days after admission into the hospital, while the morphine maintenance dosage was being stabilized. Thereafter, trazodone (50 mg; Warner Chilcott, Morris Plains, NJ) was available if participants reported having trouble sleeping.

2.10. Oral morphine maintenance

Participants were stabilized on morphine during the first 5 or 6 days after admission. Morphine was administered daily at 06.00, 11.00, 16.00 and 22.00 h. The interdose interval of morphine administration was chosen because the time course of oral morphine's effects is 4–7 h (Reisine and Pasternak, 1996), which is similar to heroin's duration of action. In addition, this interdose interval mimics the typical pattern of heroin use reported by heroin-dependent individuals. Under this maintenance schedule, the experimental sessions were conducted such that heroin administration always occurred approximately 4 h after the previous morphine dose. Stability of the morphine maintenance schedule was defined as absence of subjective and objective withdrawal effects and no change in morphine dose for at least two days prior to the start of the experimental sessions. Participants were maintained on oral morphine because it prevents withdrawal, but has minimal subjective effects in dependent individuals (Fraser et al., 1978a,b; Reisine and Pasternak, 1996).

Morphine sulfate (10 mg/5 ml liquid suspension; Roxane Laboratories, Columbus, OH) was mixed with orange juice to achieve a final fluid volume of 250 ml. Individual participants were maintained on 20, 30, 30, 30 and 40 mg q.i.d. morphine. For comparison, when used for analgesia, morphine's oral to parenteral (intramuscular, subcutaneous) potency ratio is approximately 6:1 (Reisine and Pasternak, 1996). For each individual, the initial morphine maintenance dose was chosen based on his objective response to the naloxone challenge test. Over the first few days after admission, the morphine dose was adjusted if withdrawal symptoms were present. None of the participants reported experiencing positive opioid agonist effects after receiving oral morphine. On Monday through Friday, the amount of morphine participants received depended on the amount of heroin that was administered during the sessions. Morphine was always given at the end of the sessions (i.e. at 11.00 and 16.00), approximately 60 min after heroin administration. If participants received placebo or a heroin dose up to 6.25 mg during an experimental session, they were given their full morphine maintenance dose. If participants received a dose between 6.25 and 12.5 mg/70 kg heroin, the maintenance morphine dose was reduced by 10 mg. If participants received between 12.5 and 25 mg/70 kg heroin, the maintenance morphine dose was reduced by 20 mg. Any heroin dose greater than or equal to 25 mg/70 kg resulted in 0 mg morphine.

The potency ratio between oral morphine and i.v. heroin can be derived in the following manner: for analgesia, the

oral to i.v. morphine potency ratio is 6:1 (Reisine and Pasternak, 1996) and for subjective effects, the i.v. morphine to i.v. heroin potency ratio is 2:1 (Jasinski and Preston, 1986). Although it is difficult to obtain precise potency estimates because different measures were used (analgesia versus subjective effects), a rough estimate of the oral morphine to i.v. heroin potency ratio is 12:1. The morphine dose adjustments made after experimental sessions in the present study were estimated conservatively in an attempt to keep the level of dependence throughout the study relatively constant. These dose reductions were empirically derived from data collected during a pilot study in heroin-dependent individuals. The doses prevented withdrawal symptoms, as measured by the subjective and objective withdrawal scales, on days when participants received placebo or low doses of heroin. Participants were blind to morphine and heroin doses throughout the study. If a participant received a placebo supplement (0 mg morphine), two drops of McCormick's blue food coloring were added to the orange juice to simulate the green color of the morphine/orange juice mixture. Although for safety reasons, the staff were not blind to the morphine or heroin doses administered during the sessions, the research volunteers were blind to doses. During the debriefing session at the end of the study, participants reported that they did not know that the morphine doses were adjusted according to the amount of heroin they received during the experimental sessions.

During mornings (06.00) and evenings (22.00), opioid withdrawal symptoms were assessed by a nurse using the objective opioid withdrawal scale immediately prior to oral morphine administration. In addition, participants completed the subjective opioid withdrawal scale at 06.00 and 22.00 immediately prior to oral morphine administration. Morning urine samples were collected daily and two random samples per week were screened for the presence of other illicit substances. No illicit substances were found in the participants' urines.

2.11. Statistical analyses

Progressive-ratio break points (the highest ratio that participants completed) for heroin and money, which could vary independently, were analyzed using a repeated-measures analysis of variance. Because the largest morning sample doses of heroin (25 and 50 mg/70 kg) produced measurable effects during the afternoon self-administration session, it was possible that the morning sample doses influenced responding during the afternoon self-administration session. Therefore, the progressive-ratio break points were analyzed using only the placebo, 6.25 and 12.5 mg/70 kg doses, which did not produce measurable effects at the beginning of the afternoon session. Break points were analyzed as a function of money ($10, $20, $40) and dose (placebo, 6.25, 12.5 mg/70 kg). Planned comparisons were made between $10 and $20, $10 and $40, and $20 and $40. In addition, planned comparisons of the break points at each dose were compared to placebo.

Visual analog scale ratings, opioid symptoms and task performance during the morning sample session were analyzed using a repeated-measures analysis of variance as a function of week (1st, 2nd, 3rd), dose (placebo, 6.25, 12.5, 25, 50 mg/70 kg) and test (visual analog scale questionnaire, opioid symptoms checklist: before and 4, 40, 60 and 270 min after heroin administration (the 270 min time point corresponds to the baseline ratings during the afternoon self-administration session); performance tasks: before and after heroin administration). The subjective and objective withdrawal scale data were analyzed using a repeated-measures analysis of variance as a function of week (1st, 2nd, 3rd), dose (placebo, 6.25, 12.5, 25, 50 mg/70 kg) and test (06.00, sample session baseline, sample session post-drug, self-administration session baseline, self-administration session post-drug, 22.00).

Pupil diameter measurements were analyzed using a repeated-measures analysis of variance as a function of week (1st, 2nd, 3rd), dose (placebo, 6.25, 12.5, 25, 50 mg/70 kg) and test (before and 4, 40, 60 and 270 min after heroin administration). Planned comparisons of the dose × time interaction were made (i.e. before and at each time point after heroin administration for each dose). Cardiovascular data were analyzed using a repeated-measures analysis of variance as a function of dose (placebo, 6.25, 12.5, 25, 50 mg/70 kg) and time (20 min pre-heroin baseline, drug administration, 50 min post-heroin administration). Pulse oximeter data were not analyzed statistically because three participants were tested without supplemental oxygen and two subjects were tested with supplemental oxygen. Because of procedural difficulties, the blood data were not salvageable and will not be discussed further.

Results were considered statistically significant if $p < 0.05$, using Hunyh–Feldt corrections, where appropriate.

3. Results

3.1. Self-administration

Fig. 1 shows the mean progressive-ratio break points for heroin (upper panel) and money (lower panel) as a function of heroin dose and money value. The maximal ratio completed for heroin (heroin break point value; Fig. 1, upper panel) increased as heroin dose increased ($p < 0.0001$). Planned comparisons revealed that heroin break points were lower when $20 was available, compared to $10 ($p < 0.02$). However, heroin break points were not significantly different when $40 was available, compared to $10 or $20. Heroin break points were significantly different from placebo after 12.5 mg/70 kg in combination with all money values. Although not used in the data analyses, the self-administration data using 25 and 50 mg/70 kg heroin are included in Fig. 1 to show that

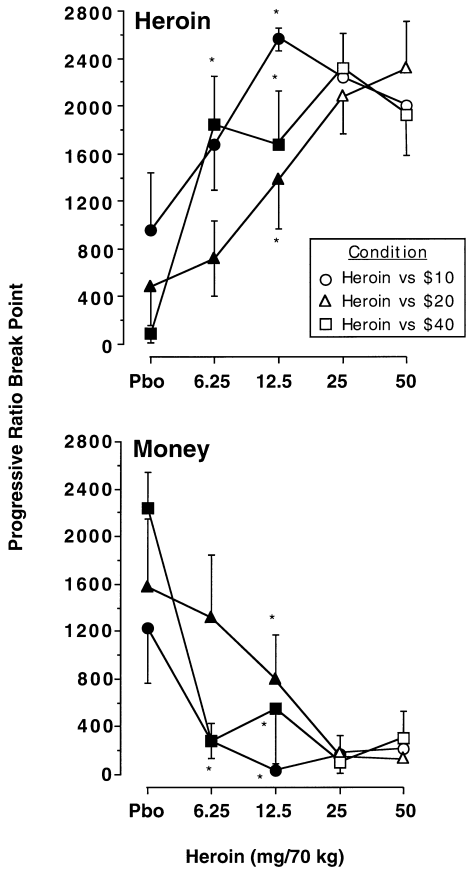

Fig. 1. Progressive-ratio break points for heroin (upper panel) and money (lower panel) as a function of heroin dose and money value ($n = 5$). Progressive-ratio break points ranged between 0 and 2800. Error bars represent ± 1 standard error of the mean (S.E.M.). Error bars around some data points were omitted for clarity. Asterisks indicate statistically significant differences from placebo. Open symbols denote the fact that the 25 and 50 mg/70 kg data were not included in the statistical analyses because of possible carry-over effects from the morning dose.

participants responded at near-maximal levels for these doses.

Consistent with the heroin break points (upper panel), the maximal progressive ratio completed for money (money break point; Fig. 1, lower panel) decreased as heroin dose increased ($p < 0.0005$). The pattern of results for money break points was identical, though opposite in direction, to the heroin break point data. That is, money break points were significantly higher when $20 was available, compared to $10 ($p < 0.05$) and money break points were not significantly different when $40 was available, compared to $10. Furthermore, money break points were significantly different from placebo after 12.5 mg/70 kg in combination with all money values ($p < 0.05$). In contrast, money break points were only significantly different from placebo after 6.25 mg/70 kg under the $40 condition ($p < 0.0006$).

3.2. Subjective effects

Fig. 2 (left panels) shows the time-course of selected visual analog scale ratings as a function of the morning sample heroin dose. Heroin produced dose-related increases in ratings of good drug effect ($p < 0.0001$) and high ($p < 0.0001$). Peak ratings of good drug effect and high occurred 4 min after administration of 6.25, 12.5 and 25 mg/70 kg heroin. 4 min after heroin administration, ratings of good drug effect and high were similar after 25 and 50 mg/70 kg heroin. However, peak ratings of good drug effect and high did not occur until 60 min after administration of 50 mg/70 kg heroin. Heroin also produced dose-related increases in ratings of stimulated ($p < 0.0009$), mellow ($p < 0.002$), energetic ($p < 0.005$), friendly ($p < 0.001$) and content ($p < 0.0002$). Ratings of good drug effect, high, stimulated, mellow and friendly were significantly different during the sample session baseline (time 0) compared to the self-administration session baseline (time 270) after administration of 50 mg/70 kg heroin ($p < 0.05$). Subjective ratings did not change as a function of week for any measure, indicating that neither tolerance nor sensitization occurred to the subjective effects produced by heroin.

Fig. 2 (right panels) shows the time-course of selected opioid symptoms that were significantly affected by the morning sample heroin dose. Heroin produced dose-related increases in ratings of itchy skin ($p < 0.0001$) and nodding ($p < 0.0001$). Doses of 12.5, 25 and 50 mg/70 kg produced reports of itchy skin, whereas only doses of 25 and 50 mg/70 kg produced reports of nodding. The only measure significantly affected by week was nodding ($p < 0.02$), where participants reported less nodding over time. In addition, heroin produced dose-related increases in coasting ($p < 0.002$), high ($p < 0.0001$), relaxed ($p < 0.02$) and drive ($p < 0.001$). The main effect of dose was also significant for total scores ($p < 0.0001$). As with the visual analog scales (left panels), opioid symptoms were still significantly elevated during the afternoon self-administration baseline, compared to the morning sample session baseline, after administration of 25 and/or 50 mg/70 kg heroin ($p < 0.05$). In contrast, all subjective ratings had returned to baseline levels prior to the self-administration session after administration of placebo, 6.25 and 12.5 mg/70 kg.

Although subjective ratings of withdrawal, as measured by total scores on the subjective opioid withdrawal scale, were elevated during the morphine stabilization period, there were no significant effects of heroin dose on total withdrawal scores during the experimental protocol (data not shown). However, craving was consistently elevated throughout the study, as indicated by near-maximal ratings of feel like shooting up now. During the third week of the study, participants reported significantly less craving at the end of the self-administration session, relative to the beginning of the self-administration session (week × test interac-

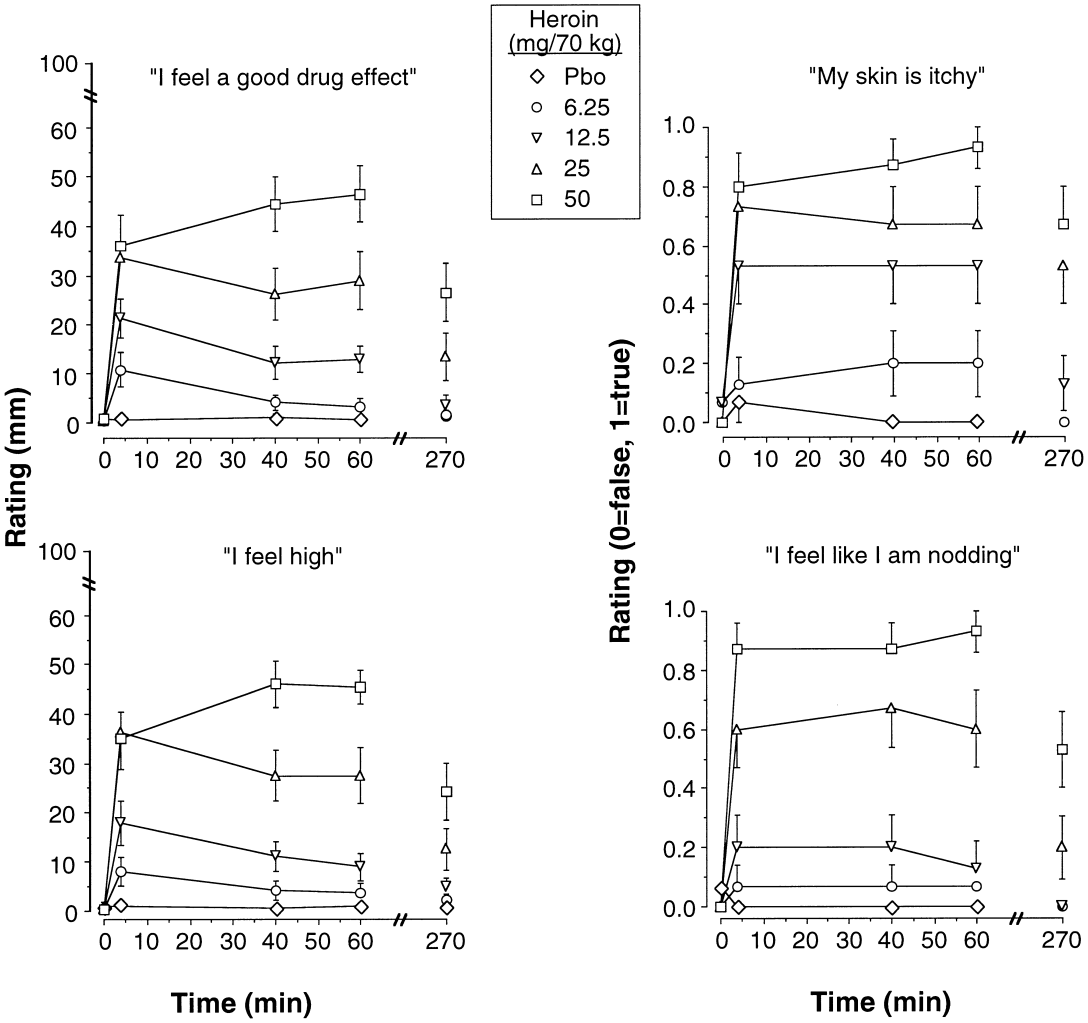

Fig. 2. Selected visual analog scale ratings (left panels) and selected items from the opioid symptom checklist (right panels) as a function of heroin dose and time ($n = 5$). Ratings ranged between 0 and 100 mm on the visual analog scale. Ratings ranged between 0 (false) and 1 (true) on the opioid symptom checklist. Data points represent the average of the three dose replications. Error bars represent ± 1 S.E.M. Error bars around some data points were omitted for clarity.

tion: $p < 0.002$). There were also small, but statistically significant increases in ratings of nauseated at the end of the self-administration session ($p < 0.04$) and small, but statistically significant increases in ratings of restless in the afternoon ($p < 0.04$). Similarly, there was a small, but statistically significant decrease in ratings of bones and muscles ache during the last 2 weeks of the experiment ($p < 0.05$). There were no significant effects of week, dose, or test on objective ratings of withdrawal, as measured by the objective opioid withdrawal scale.

3.3. Performance effects

Fig. 3 shows the effects of the morning sample heroin dose on performance of the rapid information processing task (upper left panel), digit-symbol substitution task (upper right panel) and divided attention task (lower panels). Heroin produced dose-related decreases in the number of targets (three consecutive even or odd digits) that participants correctly identified during the rapid information processing task, as indicated by a significant dose $\times$ test interaction ($p < 0.0001$) and dose-related increases in the number of targets that participants missed ($p < 0.0001$) (Fig. 3, upper left panel). The number of patterns that participants attempted ($p < 0.0001$) and completed ($p < 0.0001$) during the digit-symbol substitution task also decreased in a dose-related fashion (Fig. 3, upper right panel). The effect of week on performance of the digit-symbol substitution task was not statistically significant. Heroin produced dose-related decreases in the number of targets (appearance of a small black square) that participants correctly identified ($p < 0.004$) and dose-related increases in the number of targets that participants missed ($p < 0.003$) during the divided attention task (Fig. 3, lower left panel). In addition, heroin produced dose-related increases in tracking distance (the distance between a

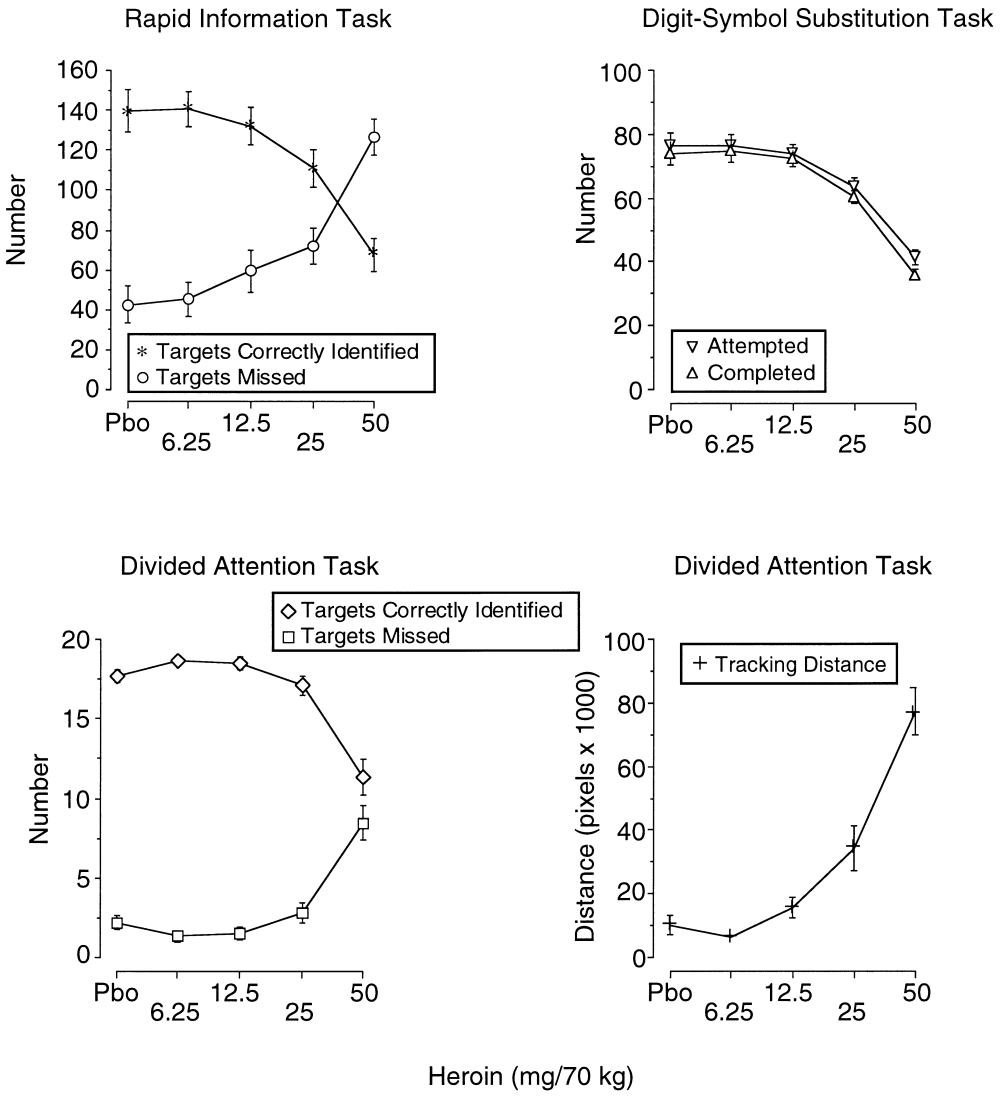

Fig. 3. Performance of the rapid information processing task (upper left panel), digit-symbol substitution task (upper right panel) and divided attention task (lower panels) as a function of heroin dose ($n = 5$). See Fig. 2 for details.

moving target and the cursor ($p < 0.0001$)) during the divided attention task (Fig. 3, lower right panel). There were significant decrements in performance of the divided attention task over the three week study (number of targets correctly identified ($p < 0.04$); the number of targets missed ($p < 0.05$) and tracking distance ($p < 0.0001$)). Performance of the repeated acquisition of response sequences task was not significantly affected by heroin.

3.4. Physiological effects

Fig. 4 (upper panel) shows the time-course of the morning sample heroin dose on pupil diameter. Heroin produced dose- and time-related decreases in pupil diameter, as indicated by a significant dose × time interaction ($p < 0.0001$). The effect of week was not statistically significant. Planned comparisons of the dose × time interaction revealed that pupil diameter significantly increased 40 min ($p < 0.009$) and 60 min ($p < 0.0002$) after administration of placebo, compared to baseline. In contrast, pupil diameter significantly decreased 4 min ($p < 0.002$), but not 40 and 60 min after administration of 6.25 mg/70 kg heroin. Pupil diameter significantly decreased at all time points after 12.5, 25 and 50 mg/70 kg heroin ($p < 0.05$). As expected, the duration of heroin's effect on pupil diameter was longer with higher doses. Pupil diameter was still significantly smaller during the self-administration session baseline, compared to the sample session baseline, after administration of 25 and 50 mg/70 kg heroin ($p < 0.0001$). After administration of placebo, 6.25 and 12.5 mg/70, pupil diameter had returned to baseline levels by the self-administration session baseline.

Fig. 4 (lower panel) shows the time-course of the morning sample heroin dose (50 mg/70 kg) on arterial

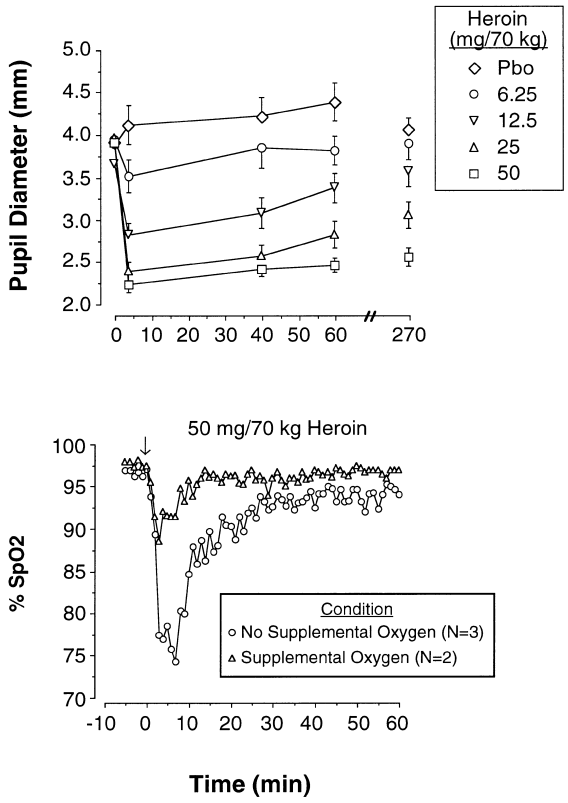

Fig. 4. Pupil diameter (upper panel) as a function of heroin dose and time ($n = 5$). Arterial oxygen saturation before and after administration of 50 mg/70 kg (lower panel) heroin as a function of time and whether subjects received supplemental oxygen ($n = 2$) or no supplemental oxygen ($n = 3$). The arrow indicates the time that heroin was administered. See Fig. 2 for details.

oxygen saturation. The first three participants were tested without supplemental oxygen and the last two participants were tested with supplemental oxygen. Although 50 mg/70 kg heroin produced a dose-related decrease in arterial oxygen saturation in all participants, the magnitude of heroin's effects was smaller in the two participants who were given supplemental oxygen. The maximal decrease in arterial oxygen saturation (74%) occurred 8 min after administration of 50 mg/70 kg heroin in the group of participants without supplemental oxygen. Although arterial oxygen saturation began to return toward baseline levels 9 min after heroin administration, it remained below baseline levels for the duration of the experimental session. These participants were behaviorally intoxicated (i.e. 'nodding') after administration of the highest dose of heroin, but they were responsive to verbal stimuli and completed all subjective-effects questionnaires and performance tasks. Nevertheless, for safety, supplemental oxygen has been provided to all subsequent research participants. Visual inspection of the data indicated that there were no differences in subjective effects or task performance by the two participants receiving supplemental oxygen, compared to the three participants who did not receive supplemental oxygen.

Heroin produced small, transient increases in diastolic pressure (approximately 3 mmHg, lasting for approximately 30 min; data not shown), as evidenced by a significant dose × time interaction ($p < 0.04$). A significant dose × time interaction was also found for heart rate ($p < 0.0001$), which was accounted for by decreases that occurred after administration of placebo, 12.5 and 25 mg/70 kg heroin. Systolic pressure and mean arterial pressure were not significantly affected by heroin.

4. Discussion

4.1. Self-administration

Results of the present experiment are consistent with studies in both humans (Mendelson and Mello, 1978; Meyer and Mirin, 1979; Mello and Mendelson, 1980) and laboratory animals (Harrigan and Downs, 1978; Mello et al., 1983, 1984) demonstrating that heroin serves as a reinforcer. Furthermore, the present results comparing $10 and $20 are consistent with previous studies showing that drug self-administration varies inversely as a function of the magnitude of an alternative reinforcer. Cocaine (Higgins et al., 1994), methadone (Stitzer et al., 1983) and alcohol (Vuchinich and Tucker, 1983) self-administration all decreased more when larger amounts of money were concurrently available, compared to smaller amounts of money. Thus, the present results with $10 and $20 extend these findings to heroin self-administration by humans. However, the effect of $40 on heroin self-administration was less clear in the present study. Under placebo conditions, participants almost always chose money, rather than drug, when $40 was available. In contrast, participants predominantly chose the drug option at all of the active heroin doses when $40 was available. Participants may have responded in this manner because it was relatively easy to earn a large amount of money with relatively little effort when $40 was available. Thus, participants could earn money easily and perhaps still get a heroin effect. Although the same could be said of the large heroin doses (i.e. it was relatively easy to earn a large amount of heroin with relatively little effort, when 50 mg/70 kg heroin was available), participants still predominantly opted for heroin.

The present results also show that the dose of the drug that is self-administered is a critical variable. Even though most participants reported during the debriefing session that it would take $40 or $50 to make them choose money over the highest heroin dose, they self-administered near-maximal amounts of heroin regardless of money value when the dose was 25 or 50 mg/70 kg. It is interesting to note that participants responded in this manner even though they still reported feeling good drug effects and high from

the morning sample dose. It is possible that the two highest doses of heroin served as 'primes' (i.e. non-contingent or experimenter-administered drug) for subsequent heroin self-administration. Previous studies in humans showed that alcohol was more likely to be self-administered after a priming dose of alcohol (De Wit and Chutuape, 1993) and studies with laboratory animals showed that priming injections of heroin or cocaine reinstated behavior previously reinforced by drug (De Wit and Stewart, 1981, 1983; Stewart and Wise, 1992; Comer et al., 1993; Worley et al., 1994). Thus, in the present study, the persistent effects of the two highest doses of heroin may have influenced the self-administration results. However, because previous studies of priming effects have not administered drug several hours prior to a self-administration session, it is unclear what role priming has under these conditions in the present study.

For the two lower heroin doses, it is less likely that priming effects influenced responding. Previous investigators have shown that in non-dependent individuals, plasma levels of heroin and its metabolites had decreased to negligible levels (< 10 ng/ml) within 2–4 h after administration of 10 mg i.v. heroin in non-dependent individuals (Jenkins et al., 1994). Furthermore, for the lower heroin doses in the present study, both pupil diameter and subjective effects had returned to baseline at the time that participants were completing the self-administration task. Although subjective effects, or lack thereof, do not necessarily predict self-administration behavior (Fischman and Schuster, 1982; Lamb et al., 1991; Fischman and Foltin, 1992), it is unlikely that the morning administration of the lower heroin doses influenced responding during the afternoon self-administration session. The rationale for this assertion is three-fold (1) plasma levels of heroin and its metabolites had likely returned to baseline, (2) a physiologic measure of heroin's effects (pupil diameter) had returned to baseline and (3) the subjective effects of heroin had returned to baseline. Therefore, it is unlikely that there were carry-over effects from the morning sample session to the afternoon self-administration session after administration of the lower heroin doses.

In addition to the potential carry-over effects from the morning dose to the afternoon, another procedural issue that has implications for interpretation of the self-administration data is the impact of the morphine dose adjustments post-session on heroin self-administration. These dose adjustments were made in an attempt to keep the level of dependence relatively constant throughout the study in order to minimize the effect of withdrawal on heroin self-administration. Given that participants did not report withdrawal effects after heroin/morphine administration during the experimental week, it is unlikely that withdrawal influenced responding. On the other hand, it is possible that the additive effects of oral morphine and i.v. heroin affected afternoon choice behavior. However, the data were orderly and dose-dependent, suggesting that this potential procedural problem is almost certainly relatively minor.

The present study demonstrates that this procedure, with a few modifications, will be useful for studying the effects of potential treatment medications on heroin's reinforcing effects. A strength of the procedure is that it is possible to separate the increases in heroin self-administration from the alleviation of withdrawal. It appears that $20 was most effective in competing with heroin under these conditions because it generated the most lawful dose–response curve: under placebo and low-dose heroin conditions, participants only rarely chose the drug option, while at higher doses, they increasingly chose drug. However, persistent drug effects produced by the two higher doses of heroin preclude comparisons of self-administration between the high and low dose conditions. In future studies, a longer intersession interval and lower doses will be used to avoid the possibility of carry-over effects.

4.2. Subjective effects

Heroin produced dose-related increases in visual analog scale ratings of good drug effect, high, mellow, stimulated, energetic, friendly, and content. These results are similar to studies using non-dependent, opioid-experienced users showing that i.v. heroin doses ranging between 0 and 10 mg/70 kg produced significant increases in subjective ratings of euphoria (elevated morphine–benzedrine group scores on the Addiction Research Center Inventory), liking and relaxed (Martin and Fraser, 1961; Jasinski and Preston, 1986). The present results also provide further information regarding the time course of these effects, demonstrating that peak subjective ratings occur as soon as 4 min after i.v. heroin administration. The increases in visual analog scale ratings of stimulated and energetic in the present study are consistent with studies using other mu agonists (e.g. Zacny et al., 1994; Foltin and Fischman, 1995), as well as with studies using laboratory animals showing that morphine-like drugs increase locomotor activity (e.g. Elmer et al., 1995; Kuribara, 1995). Furthermore, in the present study, participants reported dose-related increases in ratings of itchy skin, nodding and coasting. These results are generally consistent with previous studies in which i.v. heroin produced dose-related increases in these measures (Martin and Fraser, 1961; Jasinski and Preston, 1986). However, higher doses were required to produce these effects in the present study, which presumably reflects the fact that participants in the present study were tolerant to the effects of heroin. Certain symptoms, such as stomach turning and soap box were reported in non-dependent individuals (Martin and Fraser, 1961; Jasinski and Preston, 1986), but not in the current study using opioid-dependent individuals. In general, participants did not report opioid withdrawal effects during experimental sessions.

4.3. Performance effects

Heroin produced significant, dose-related impairments in performance of the rapid information processing task, the digit-symbol substitution task, and the divided attention task, but not the repeated acquisition of responses sequences task in the present study. Several previous studies showed that opioids such as hydromorphone, pentazocine, butorphanol, nalbuphine or buprenorphine, produced no or relatively few impairments in digit-symbol substitution task or memory task performance (e.g. Preston et al., 1989, 1992; Strain et al., 1992; Pickworth et al., 1993; Foltin and Fischman, 1995). However, other studies using morphine (Foltin and Fischman, 1992; Zacny et al., 1994) or heroin (Jenkins et al., 1994) showed significant impairments in performance. The discrepancy between these results may in part be due to differences in route of administration, since opioids administered intravenously (Foltin and Fischman, 1992; Pickworth et al., 1993; Jenkins et al., 1994; Zacny et al., 1994) typically showed more robust decrements in performance than opioids administered intramuscularly or sublingually (Preston et al., 1989, 1992; Strain et al., 1992; Foltin and Fischman, 1995).

Furthermore, although previous studies showed that i.v. morphine produced modest, but statistically significant decreases in performance speed, but not accuracy (Foltin and Fischman, 1992; Zacny et al., 1994) in non-dependent individuals, substantial decreases in both speed and accuracy occurred after administration of i.v. heroin in the present study. This discrepancy may be due to differences in drug and/or dose. Performance of the repeated acquisition of responses sequences task, which is designed to assess learning and memory, was not affected by i.v. heroin. Other studies have shown that, in humans, delayed, but not immediate, memory is impaired by i.v. morphine (Kerr et al., 1991). In laboratory animals, a repeated-acquisition and performance task has been used to assess learning and performance. In this procedure, intramuscular heroin produced dose-related decreases in overall response rate (Moerschbaecher et al., 1983). However, accuracy was only affected during the learning component and only at doses that produced substantial decreases in response rate. Thus, heroin and other mu-receptor-selective opioids (Moerschbaecher et al., 1983; Pakarinen et al., 1995) appear to have little effect on learning and memory. In a recent review of the effects of opioids on psychomotor and cognitive functioning, Zacny et al. (1994) reported that only 8 studies have assessed the effects of heroin on task performance. Of those, impairments in performance only occurred in individuals with no known history of drug abuse. Impairments in performance were not found in studies evaluating opioid-dependent individuals. Thus, Zacny (1995) concluded that heroin may have minimal effects on functioning in opioid-dependent individuals. The present study, using a number of different performance tasks, provides the first clear evidence that heroin does produce dose-related decrements in psychomotor task performance in opioid-dependent individuals.

4.4. Physiological effects

Heroin produced a time- and dose-related miosis, which is a classic effect of mu-receptor-selective opioids (e.g. Martin and Fraser, 1961; Jasinski and Preston, 1986; Jenkins et al., 1994). The time-course of both miosis and subjective effects was generally similar in the present study. The time-course of miosis and subjective effects was also similar in a previous study using non-dependent individuals (Jasinski and Preston, 1986). However, the duration of effect was different between the present study and that reported by Jasinski and Preston (1986). In the present study, the miotic effect produced by 12.5 mg/70 kg heroin had returned to baseline levels by approximately 4.5 h, whereas in non-dependent individuals, the miotic effect produced by 10 mg/70 kg was still evident after 12 h. The reason for this discrepancy is unclear. Heroin also produced a time- and dose-related decrease in arterial oxygen saturation in the present study. Up to doses of 25 mg/70 kg, the decreases in arterial oxygen saturation were relatively minor in participants tested without supplemental oxygen. However, a dose of 50 mg/70 kg produced a marked decrease in arterial oxygen saturation. For safety, supplemental oxygen was provided to the last two participants and, as expected, arterial oxygen saturation levels increased relative to participants tested without supplemental oxygen. During the debriefing session, most participants reported that the 50 mg/70 kg dose was equivalent to approximately 2 'bags' of heroin ($10/bag) purchased on the street. The fact that participants also reported that they commonly injected this amount at once indicated that there may be a relatively small difference between doses of street heroin that are commonly self-administered and a potentially harmful dose of heroin.

In summary, the present results demonstrate that an alternative reinforcer was effective in reducing low-dose heroin self-administration by morphine-maintained human research volunteers in a controlled, inpatient laboratory setting. These results are consistent with a previous clinical study demonstrating that supplemental heroin use decreased in methadone-maintained individuals when money was the alternative reinforcer (i.e. participants could receive $15 for morphine-free urines; Stitzer et al., 1980). The data are also consistent with a large body of research demonstrating that alternative reinforcers in general are effective in reducing drug self-administration (for review, see Carroll, 1996). Importantly, the present results show that the alternative reinforcer was only effective in reducing heroin self-administration under certain conditions (i.e. when the available i.v. heroin dose was relatively low). Given the utility and sensitivity of our procedure for studying heroin self-administration, future studies will evaluate the effects of pharmacological, as well as com-

bined pharmacological and non-pharmacological, interventions for reducing heroin abuse.

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