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Discrimination of Butorphanol and Nalbuphine in Opioid-Dependent Humans[1]

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PRESTON, K. L., G. E. BIGELOW AND I. A. LIEBSON. *Discrimination of butorphanol and nalbuphine in opioid-dependent humans*. PHARMACOL BIOCHEM BEHAV 37(3) 511–522, 1990.—The purpose of the study was to evaluate the agonist and antagonist stimulus properties of the mixed opioid agonist antagonists butorphanol and nalbuphine in opioid-dependent subjects. Opioid-dependent volunteers (methadone 30 mg/day, PO) were trained in a three-choice drug discrimination procedure to discriminate between the effects of saline (2 ml), hydromorphone (10 mg/70 kg) and naloxone (0.15 mg/70 kg) administered IM. Subjects earned monetary reinforcement for correctly identifying the training drugs by letter code. Other subjective, behavioral and physiological measures were also collected. Hydromorphone and naloxone increased drug-appropriate responses and other characteristic subjective effects measures. Butorphanol and nalbuphine produced increases in naloxone-appropriate discrimination responding and in those subjective effect measures increased by naloxone. Butorphanol produced greater than 80% naloxone-appropriate responding at 1.05 mg/70 kg; nalbuphine produced 100% naloxone-appropriate responding at 2.1 mg/70 kg. Neither butorphanol nor nalbuphine showed opioid agonist-like effects in these subjects maintained at moderate levels of physical dependence. In opioid-dependent subjects, the stimulus effects of butorphanol and nalbuphine are antagonist-like.

Drug discrimination Opioids Hydromorphone Naloxone Butorphanol Nalbuphine Human subjects

THE mixed agonist-antagonist opioids are a group of compounds that under some conditions (e.g., in the absence of appreciable physical dependence on opioids) produce agonist-like effects and under other conditions (e.g., in the presence of significant physical dependence) produce antagonist-like effects. For example, Jasinski and his colleagues (10) showed that profadol and propiram produced morphine-like subjective and physiological effects in nondependent subjects, suppressed abstinence in subjects dependent on a relatively low dose of morphine (60 mg/day, SC), and precipitated withdrawal-like effects in subjects dependent on a higher dose of morphine (240 mg/day, SC). The purpose of the present study was to examine two other agonist-antagonist opioids, butorphanol and nalbuphine, for evidence of agonist-like and/or antagonist-like stimulus effects in subjects with moderate levels of physical dependence.

In nondependent subjects, butorphanol acts as an opioid agonist (5); it is marketed in the United States as an opioid analgesic. However, neither agonist nor antagonist effects of butorphanol have been documented in morphine-dependent humans. Butorphanol failed to significantly suppress abstinence signs in withdrawn morphine-dependent (60 mg/day SC) human subjects (7). In doses up to 8 mg, butorphanol precipitated only mild, nondose related abstinence signs (equivalent to nalorphine 1.5 mg) in nonwithdrawn subjects dependent on morphine 120 mg/day; however, increases in the doses of butorphanol tested were prevented by disturbing subjective effects similar to those produced by single doses of butorphanol in nondependent subjects, suggesting that some of the effects seen were due to agonist actions (7). Butorphanol has, however, been shown to precipitate withdrawal in methadone-dependent humans (16).

Nalbuphine also acts as an opioid agonist in nondependent subjects (2) and is marketed in the United States as an opioid analgesic. The antagonist activity of nalbuphine in morphine-dependent humans has been more broadly demonstrated than has that of butorphanol. In subjects dependent on 60 mg of morphine SC per day, Jasinski and Mansky (8) found that nalbuphine was ¼ as potent as nalorphine in precipitating abstinence. Nalbuphine has also been shown to precipitate withdrawal in methadone-dependent humans (18). Agonist effects of nalbuphine (i.e., suppression of withdrawal from morphine) in opioid-dependent humans have not been tested.

The present study uses a behavioral drug discrimination methodology to assess the relative agonist versus antagonist actions of butorphanol and nalbuphine in opioid-dependent human volun-

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teers. We have previously shown that methadone-dependent subjects can be trained to discriminate between the effects of hydromorphone and naloxone (14). The profiles of effects indicated that hydromorphone produced typical opioid agonist-like effects, while naloxone produced precipitated withdrawal in these methadone-dependent subjects. When tested with various doses of the training drugs, hydromorphone and naloxone produced dose-related increases in their respective drug-appropriate discrimination responses and in characteristic subjective responses. There was no cross-generalization between hydromorphone and naloxone in these subjects. This procedure was, therefore, shown to be sensitive to both opioid agonist-like and antagonist-like effects.

In the present study the stimulus effects of butorphanol and nalbuphine in subjects with moderate levels of physical dependence were examined for agonist-like and antagonist-like effects. Methadone-dependent subjects were trained to discriminate among saline, hydromorphone and naloxone. Subjects were then tested with various doses of hydromorphone, naloxone, butorphanol and nalbuphine. Dependent variables included measures of drug discrimination behavior as well as more traditional subjective effect measures, and psychomotor performance and pupil diameter measures.

METHOD

Subjects

The participants were five male physically dependent methadone maintenance patients who ranged in age from 29 to 51 years (mean 39 years) and weighed between 72 and 120 kg (mean 87 kg). The subjects reported prior narcotic addiction of 8 to 34 years duration (mean 17 years) and participation in a methadone maintenance program for 2 months to 16 years (mean 5 years). On the basis of physical examination, history, and routine laboratory chemistries, participants were found to be in good health and without significant psychiatric disturbance other than their drug abuse. Subjects were maintained on orally administered methadone hydrochloride (Methadose, Mallinckrodt, St. Louis, MO) 30 mg daily. Methadone doses were given at 1:20 p.m. daily, approximately 22 hours prior to each experimental session. This study was approved by the appropriate Institutional Review Boards for human research; subjects gave their written informed consent prior to beginning the study and were paid for their participation.

Setting

Subjects participated while residing on an eight-bed behavioral pharmacology research ward previously described (4). The research ward contained a nursing station, patient bedrooms, recreational area, dining area and experimental session rooms. Various recreational, reading, and craft materials and exercise equipment were available to the subjects at all times other than during experimental sessions or overnight. Research nursing staff were present 24 hours each day.

Drugs

The training drugs were saline (2 ml), hydromorphone hydrochloride 10 mg/70 kg, and naloxone hydrochloride 0.15 mg/70 kg. Dose-response generalization testing was conducted on hydromorphone, naloxone, butorphanol and nalbuphine. Commercially available preparations of each drug were used: hydromorphone hydrochloride (10 mg/ml; Knoll Pharmaceuticals, Whippany, NJ); naloxone hydrochloride (0.4 mg/ml; Dupont, Wilmington, DE); butorphanol tartrate (2 mg/ml; Bristol Laboratories, Syracuse, NY); nalbuphine hydrochloride (10 mg/ml; Du Pont Pharmaceuticals, Wilmington, DE). All doses were calculated on the basis of the salts. Appropriate volumes of each drug were diluted to the desired concentration with bacteriostatic saline; doses were given IM in a constant volume of 2.0 ml in the deltoid muscle. Training drugs were identified to subjects only by arbitrary letter codes (A, B, and C). For each subject the drug letter codes associated with each of the training drugs were randomly determined, but remained unchanged throughout the protocol. All doses of drugs were given on a per 70 kg basis. For generalization testing doses for each drug were selected based on previous studies (14, 16, 18). Drug was administered under double-blind conditions.

General Method

Subjects were informed that they would receive drugs with opioid properties and opioid-blocking properties, that they might receive various psychoactive drugs that could have sedative or stimulant properties, and that the study involved evaluation of their ability to discriminate one drug from another and evaluation of the subjective, behavioral and physiological effects of those drugs. To reduce the possibility that subjects would receive instructions or explanations which might confound the results, staff were explicitly instructed to refrain from discussing the experiment with subjects, except to provide an objective description of the routines and procedures which the subject must follow. Prior to the start of the study, subjects participated in one or two practice sessions, in which no drugs were given, to familiarize them with the procedures. The study then proceeded in three phases, with sessions conducted daily. Sessions were conducted in the same manner in all three phases except for the letter code information that was provided to the subject either before or after each session as described below.

Discrimination training was conducted in sessions 1–6, during which the subject received, in randomized block order, two sessions of exposure to each of the three training conditions—saline, hydromorphone 10 mg/70 kg, and naloxone 0.15 mg/70 kg. During these training exposures each drug was identified to the subject by letter code *prior* to drug administration. The subject was instructed to attend carefully to the drug effects and to try to discriminate precisely among them; he was informed that in each session he would be able to earn money by correctly identifying the administered drug by letter code.

In sessions 7–12 acquisition of the discrimination was tested by exposing the subject to the training doses of each of the three training compounds twice in randomized block order. The purpose of these sessions was to determine whether the subject could correctly identify the training drug/doses by letter code. During these and all subsequent exposures to the training doses the subject received feedback about the code of the administered training drug *after* the session. This test-of-acquisition procedure was also repeated intermittently in randomly selected sessions between test sessions during the subsequent testing phase to provide continued retraining and to ensure continued correct discrimination.

Beginning with session 13, a series of test sessions was conducted. Test sessions were interspersed randomly with test-of-acquisition sessions in which one of the training drugs/doses were given. During this testing phase dose response curves for the two training drugs were determined followed by dose-response curves for butorphanol and nalbuphine (in that order); doses of active drug in each dose-response curve were administered in a randomized sequence. Following each test session the subject did not receive feedback about the correct drug identification but was

TABLE 1

OUTLINE OF EXPERIMENTAL SESSION AND ORDER OF PRESENTATION OF MEASURES

Time (min)	
−20	Physiological measures temperature, pulse, respiration rate, blood pressure, pupil diameter
−15	Predrug measures ARCI short form, DSST, adjective rating scales
0	Drug administration
20	Postdrug measures—Cycle 1 Subjective effect measures (ARCI short form, Visual analog scales, Pharmacological class questionnaire, Adjective rating scales) DSST
30	Pupil Diameter
40	Postdrug measures—Cycle 2 (same as Cycle 1)
50	Pupil Diameter
60	Postdrug measures—Cycle 3 Operant response discrimination measure DSST Subjective effect measures (ARCI short form, Visual analog scales, Pharmacological class questionnaire, Adjective rating scales) Discrete choice discrimination measure Point distribution discrimination measure
70	Pupil Diameter
80	Postdrug measures—Cycle 4 (same as Cycle 1)
90	Physiological measures temperature, pulse, respiration rate, blood pressure, pupil diameter
100	Envelope containing the letter-code identity of the drug was opened and read to the subject.
120	Methadone dose given.

informed that it had been a test session and that the drug code could not be revealed.

All five subjects completed the entire study. At the conclusion of the experiment each subject's earnings were proportional to the accuracy of his discrimination throughout the study and were paid to each subject after he was discharged from the research ward. Earnings for the study averaged $876.26, 46% of which was contingently earned for correct discrimination responses.

Apparatus

A Commodore 64 microcomputer (Commodore Business Machines, Inc., West Chester, PA) was programmed to present all questionnaires and performance tests in a prearranged and timed sequence. The Commodore 64 microcomputer was interfaced to an Apple IIe microcomputer (Apple Computer, Cupertino, CA) that collected, saved to disk, and printed the data during each session. The subject indicated his responses on a numeric key pad.

Experimental Session

Daily sessions began at 11:00 a.m. An outline of the sessions is given in Table 1. At the beginning of each experimental session (prior to drug administration), baseline physiological measures were recorded, and the subject completed two self-report questionnaires [Addiction Research Center Inventory (ARCI) and adjective rating scales] and a psychomotor performance task in the experimental room. The scheduled drug was then given by IM injection by the nursing staff. During the initial training sessions the subject was informed of the drug's identifying letter code at the time of injection. The subject remained under medical observation for twenty minutes, and then returned to the experimental room to

TABLE 2

SUMMARY OF THE EFFECTS OF THE TRAINING DRUGS DURING TRAINING AND/OR TEST OF ACQUISITION SESSIONS

	Hydromorphone (10 mg/70kg)	Saline (2.0 ml)	Naloxone (0.15 mg/70 kg)
Discrimination Measure (% Correct)			
Point Distribution	100.0 (0.0)	87.5 (11.7)	100.0 (0.0)
Operant Responding	100.0 (0.0)	87.5 (11.7)	100.0 (0.0)
Discrete Choice	100.0 (0.0)	87.4 (11.7)	100.0 (0.0)
Visual Analog Scales			
Drug Effect	206.4 (24.5)*	55.8 (17.1)	247.6 (19.0)*
High	172.1 (22.8)*	47.2 (12.4)	35.8 (5.1)
Liking	222.9 (25.0)*	86.2 (33.2)	32.9 (6.1)
Good Effects	229.1 (24.8)	104.9 (33.5)	30.9 (3.4)
Bad Effects	44.9 (8.8)	38.0 (7.0)	296.9 (21.0)*
Sick	43.9 (11.2)	37.4 (8.6)	277.2 (27.8)*
Like hydromorphone	365.2 (6.9)*	54.2 (24.4)	32.6 (7.9)
Like naloxone	20.4 (3.3)	20.4 (3.7)	342.6 (13.8)*
Like saline	25.7 (5.0)*	317.7 (31.8)	33.7 (7.5)*
Adjective Rating Scales			
Agonist	22.6 (5.2)	2.3 (1.8)	13.3 (4.2)
Antagonist	3.4 (1.4)	1.1 (2.0)	59.9 (5.3)*
Mixed Agonist-Antagonist	4.0 (1.0)	3.2 (1.5)	23.8 (4.8)
ARCI			
MBG (euphoria) scale	2.9 (1.6)	−2.8 (1.3)	−24.0 (6.9)
LSD (dysphoria) scale	5.8 (1.6)	2.2 (1.3)	21.6 (5.6)
PCAG (sedation) scale	2.1 (1.1)	0.3 (0.9)	27.3 (4.6)*
Physiological Measures			
Heart Rate (beats/min)	1.0 (2.0)	−3.9 (2.0)	−4.9 (1.6)
Blood Preasure			
Systolic (mmHg)	2.2 (3.5)	−0.2 (2.6)	0.2 (3.8)
Diastolic (mmHg)	6.4 (2.7)	−0.7 (2.5)	−0.2 (2.3)
Respiration Rate (breaths/min)	0.0 (0.6)	0.9 (0.6)	−0.5 (0.7)
Temperature (°F)	0.04 (0.30)	0.23 (0.24)	−0.06 (0.15)
Pupil Diameter (mm)	−0.97 (0.11)*	−0.14 (0.13)	0.27 (0.14)*
Psychomotor Performance			
DSST — Number Correct	−1.8 (3.0)	−1.6 (3.0)	−16.9 (4.8)
DSST — Number Attempted	−2.2 (2.5)	−1.8 (2.5)	−14.2 (3.8)

Values represent mean (S.E.M.) sum across successive observations in a session of the actual values or change from predrug values in each of four subjects. Discrimination measures are based on two and all other measures are based upon four sessions with each drug per subject. Asterisks indicate significant differences ($p<0.05$) from saline.

complete the postdrug discrimination, subjective effect and performance testing. Postdrug testing consisted of four consecutive 20 minutes cycles. The third and fourth cycles contained assessments of drug discrimination; all cycles contained assessments of subjective effects (Addiction Research Center Inventory, adjective rating scales, visual analog scales and pharmacological class question) and psychomotor performance. These are described in detail below. The 20 minutes allotted for the completion of the self-report questionnaires, discrimination measures, and psychomotor performance task in each cycle was ample for all subjects. At the end of the session the staff again recorded physiological measures. A sealed envelope was then opened, and the staff informed the patient of the letter-code identity of the administered drug and the amount earned in the session; following test sessions the card said only that the session had been a test session and that the identity of the drug could not be revealed.

Discrimination Procedures

Drug discrimination data were collected in three ways: 1) Discrete Choice—the subject named by letter code (A, B, or C) the drug he thought he had received; (2) Point Distribution—the subject distributed 50 points between one or more of the three drug choice alternatives depending upon how certain he was of the identity of the administered drug; 3) Operant Responding—the subject responded on a fixed-interval 1-sec schedule on computer keys designated with drug letter codes to earn points for 8.5 minutes; points (displayed on the computer screen) could be earned (at a maximum rate of one per sec) for each of the three choice drugs by pressing the key corresponding to that drug. Whenever the subject switched from one key to another a 10-sec delay occurred during which key presses earned no points. The operant responding discrimination measure was included because operant responding is commonly used in animal drug discrimination studies. In each of these three procedures only correct responses were converted to monetary reinforcement for the subject.

The maximum amount of contingent payment available per session was approximately $10.00. Actual payment for correct responses was determined according to the following schedule:

TABLE 3

RESULTS OF THE DRUG CLASS QUESTIONNAIRE DURING TRAINING AND TEST OF ACQUISITION SESSIONS (NUMBERS 1–12)

	Hydromorphone (10 mg/70 kg)	Saline (2.0 ml)	Naloxone (0.15 mg/70 kg)
Blank (Placebo)	3.1	93.8	0
Opioid	93.8	0	0
Opioid Antagonist	0	0	100
Benzodiazepine/Barbiturate	3.1	6.2	0

Values represent % total identifications for four observations/session for four subjects tested four times with each drug condition. No responses were given for other drug classes listed on the questionnaire.

discrete choice measure—$1.50/cycle ($3.00/session); point distribution measure—$0.03/point (50 points/cycle—$1.50) ($3.00/session); operant response measure—$0.004/point (approximately 500 points/cycle earned—$2.00) (approximately $4.00/session). Subjects were not informed as to the precise monetary value of each response but were told that a bonus payment of up to $10.00 was available in each session and that the bonus was determined by the number of correct responses. Earnings on test sessions were determined by the discrimination accuracy of the most recent test-of-acquisition session responding. Earnings were reported to the subjects at the end of each experimental session.

Subject- and Observer-Rated Measures

Four questionnaires were completed: 1) visual analog scales, 2) a pharmacological class questionnaire, 3) an adjective rating scale, and 4) a shortened form of the ARCI. On the visual analog scales, the subject rated his current degree of "high" and "sick," the degree of "any drug effect," "good effects," "bad effects," and "liking" of the drug effects, and the similarity of the drug effect to each of the training drugs (identified by letter code) by placing an arrow along a 100-point line marked at ei-

TABLE 4

SUMMARY OF GENERALIZATION TESTING

	Hydromorphone 0, 2.5, 3.5, 5, 7, 10 mg/70 kg	Naloxone 0, 0.0375, 0.053, 0.075, 0.105, 0.15 mg/70 kg	Butorphanol 0, 0.375, 0.53, 0.75, 1.05, 1.5 mg/70 kg	Nalbuphine 0, 1.05, 1.5, 2.1, 3 mg/70 kg
Discrimination Measures				
----Discrete Choice				
Like hydromorphone	<0.001 ↑	—	—	—
Like naloxone	0.022 ↓	0.001 ↑	0.015 ↑	0.058 ↑
Like saline	0.001 ↓	0.001 ↓	0.019 ↓	0.001 ↓
----Point Distribution				
Like hydromorphone	0.001 ↑	—	—	—
Like naloxone	—	<0.001 ↑	<0.001 ↑	0.006 ↑
Like saline	0.001 ↓	<0.001 ↓	<0.001 ↓	0.006 ↓
----Operant Responding				
Like hydromorphone	0.001 ↑	—	—	—
Like naloxone	—	<0.001 ↑	<0.001 ↑	0.006 ↑
Like saline	0.001 ↓	<0.001 ↓	<0.001 ↓	0.006 ↓
Visual Analog Scales				
Like hydromorphone	0.006 ↑	—	—	—
Like naloxone	—	<0.001 ↑	0.001 ↑	0.002 ↑
Like saline	0.010 ↓	<0.001 ↓	0.002 ↓	0.004 ↓
Drug Effect	0.011 ↑	<0.001 ↑	0.014 ↑	0.022 ↑
High	0.003 ↑	—	—	—
Liking	0.027 ↑	—	—	—
Good Effects	0.011 ↑	—	—	—
Bad Effects	—	<0.001 ↑	0.014 ↑	0.012 ↑
Sick	—	<0.001 ↑	0.021 ↑	0.006 ↑
Adjective Rating Scales				
Agonist	—	—	—	—
Antagonist	—	0.011 ↑	0.025 ↑	—
Mixed	—	—	0.057 ↑	0.030 ↑
ARCI				
MBG	—	0.016 ↓	—	—
LSD	—	—	—	—
PCAG	—	0.007 ↑	—	—

Statistical significance of dose effects for each drug was determined by repeated measures, one factor analyses of variance. Values represent p values; arrows indicate directions of drug effect relative to placebo. N = 5.

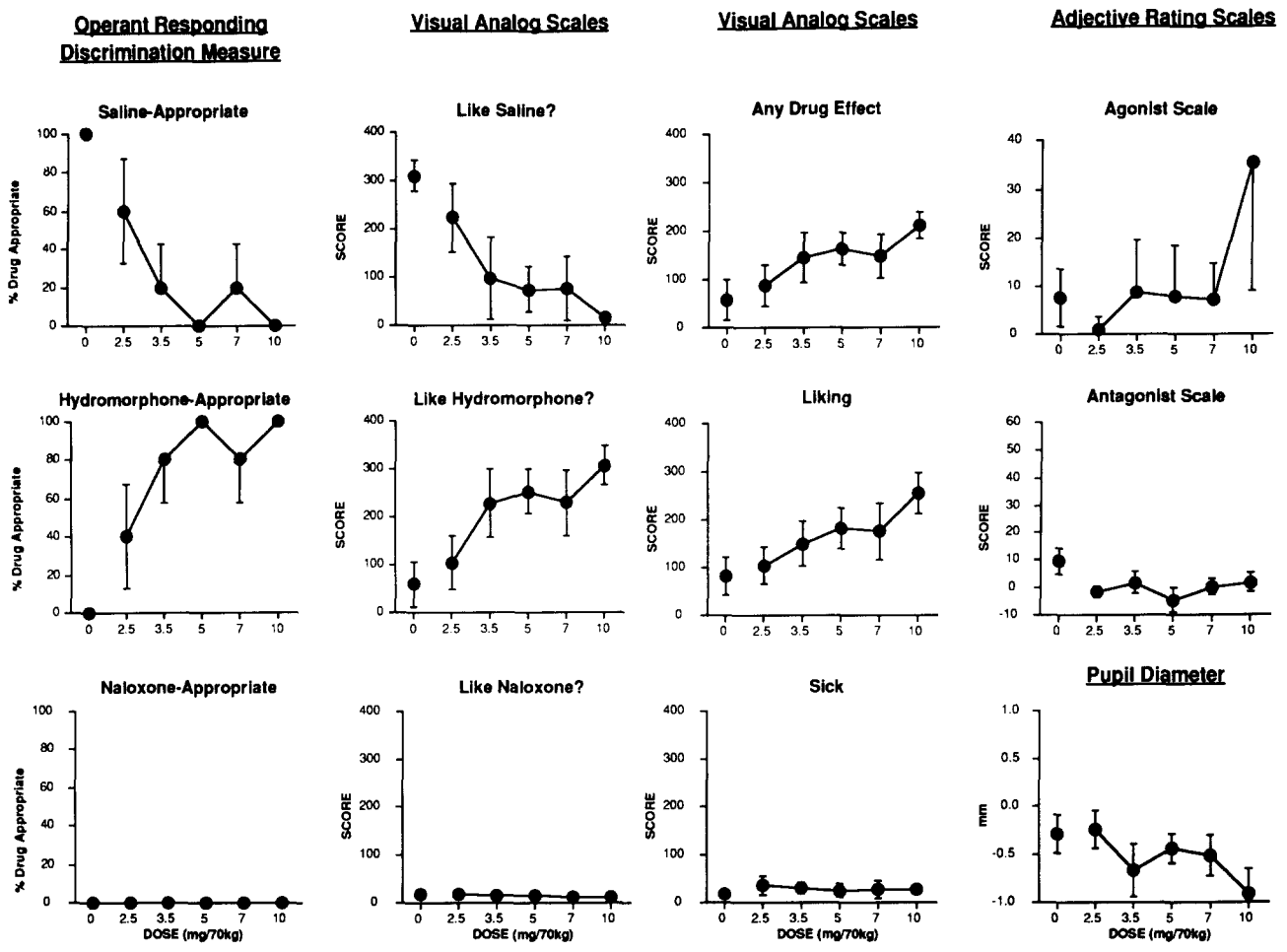

FIG. 1. Dose-response curves of selected measures produced by test doses of hydromorphone and saline in opioid-dependent subjects trained to discriminate between hydromorphone 10 mg/70 kg, saline 2.0 ml, and naloxone 0.15 mg/70 kg. On the operant responding discrimination measure each point is the mean ± 1 S.E.M. based upon two observations following administration of each dose one time in each of five subjects. For all other measures each point is the mean ± 1 S.E.M. of the sum of four observations/session following administration of each dose one time in each of five subjects. The S.E.M. is not shown where it is less than the radius of the symbol.

ther end with "none" and "extremely." On the pharmacological class questionnaire, the subject categorized the drug effect as being most similar to one of 10 classes of psychoactive drugs. The questionnaire provided descriptive titles for and examples of each of the following classes: placebo, opiates, phenothiazines, barbiturates and sleeping medications, opiate antagonists, antidepressants, hallucinogens, benzodiazepines, stimulants, and phencyclidine. The adjective rating scale consisted of 32 items which the subject rated on a 5-point scale from 0 (no effect) to 4 (maximum effect). The items in the adjective list were divided into 3 subscales: the Agonist scale (13 adjectives associated with morphine-like effects), the Antagonist scale (10 adjectives associated with withdrawal-like effects), and the Mixed Agonist-Antagonist Opioid scale (9 adjectives describing side-effects of currently marketed mixed agonist-antagonist narcotic analgesics). Items in the individual scales were as follows: Agonist Scale—skin itchy, turning of stomach, nodding, relaxed, pleasant sick, talkative, heavy or sluggish feeling, dry mouth, drive, carefree, drunken, good mood, energetic; Antagonist Scale—flushing, sweating, sleepy, watery eyes, runny nose, chills, shaky, gooseflesh, restless, agitated; Mixed Agonist-Antagonist Scale—coasting or spaced out, tingling, tired, headache, floating, confused, lightheaded, depressed, numb. The ratings of the individual items in the Agonist, Mixed Agonist-Antagonist, and Antagonist scales were summed to determine a single total score for each scale. The short form of the ARCI consisted of 49 true/false questions and contained five major subscales: Morphine-Benzedrine Group (MBG) (a measure of euphoria); Pentobarbital, Chlorpromazine, Alcohol Group (PCAG) (a measure of sedation); Lysergic Acid Diethylamide (LSD) (a measure of dysphoric changes); and Benzedrine Group and Amphetamine scales (empirically derived amphetamine-sensitive scales) (12).

Physiological and Psychomotor Measures

Physiological effects monitored included respiration, heart rate, blood pressure, oral temperature, and pupil diameter. Pupil diameter was measured from photographs taken in constant ambient room lighting using a Polaroid camera with 3× magnification. The psychomotor performance test used was a computerized ver-

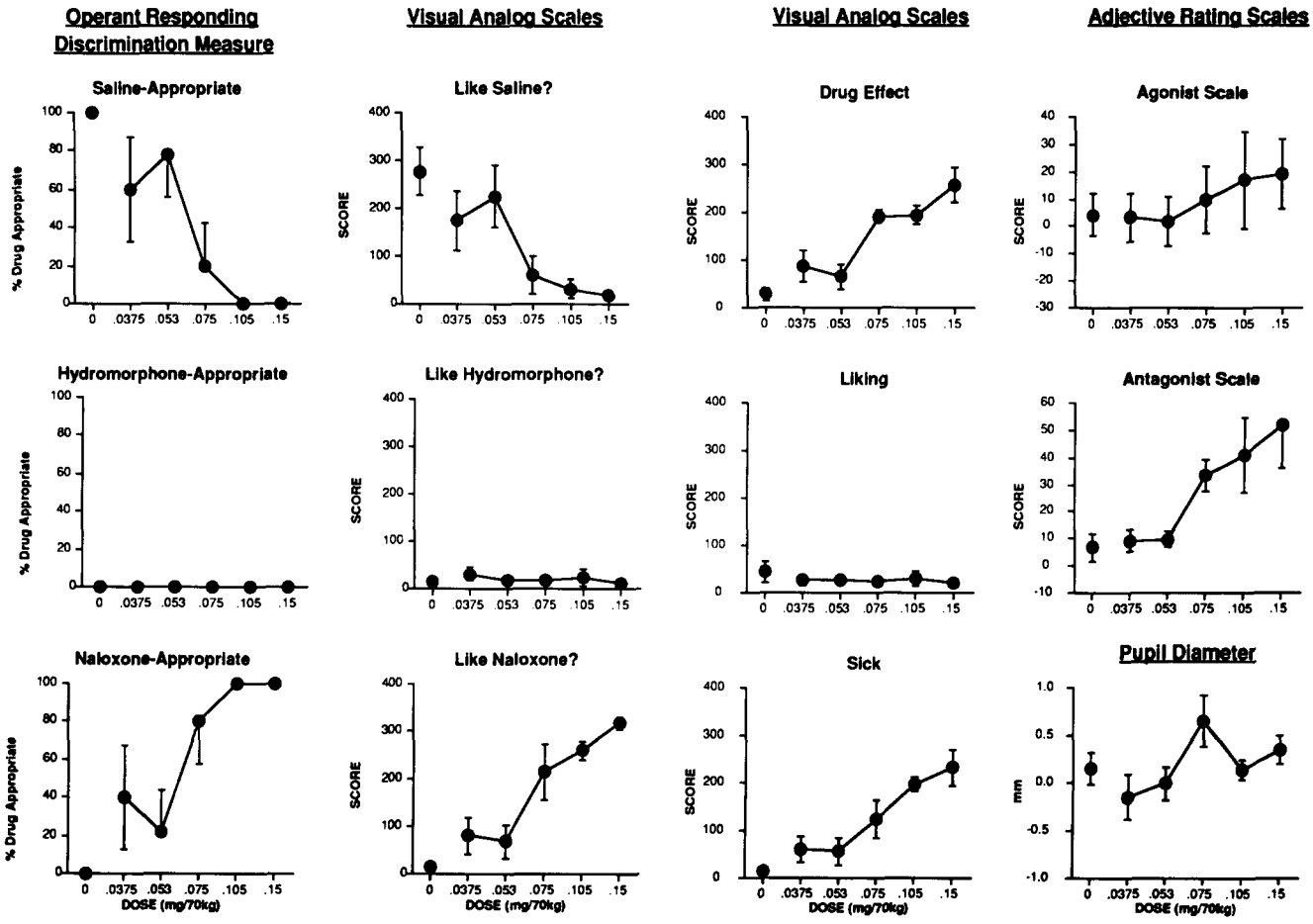

FIG. 2. Dose-response curves of selected measures produced by test doses of naloxone and saline in opioid-dependent subjects trained to discriminate between hydromorphone 10 mg/70 kg, saline 2.0 ml, and naloxone 0.15 mg/70 kg. See Fig. 1 caption for details.

sion of the Digit Symbol Substitution Test (DSST) which was developed in our laboratory (13).

Data Analysis

Data reported are means across subjects. For each subject the visual analog scales are the sum across the session (four postdrug presentations/session); ARCI, adjective rating scales, and DSST scores are the sum of changes from predrug scores (four postdrug presentations/session), and physiological measures are the change from predrug scores (one postdrug measure/session). The results of the discrimination data are reported as percent correct identifications over the entire session (two postdrug presentations/session). Subjective and physiological data from the training and test of acquisition sessions are based on four exposures to each training drug in sessions 1–12, and results of the discrimination measures are based on two exposures to each training drug in sessions 7–12 (the test-of-acquisition phase). Two-factor, repeated measures analyses of variance (with factors of training drug and session) were conducted on the training and test-of-acquisition phases. Post hoc analyses were conducted using Tukey Tests. Generalization dose response functions for each active drug (including its appropriate saline control session) were analyzed two ways for all variables: 1) two-factor, repeated measures analyses of variance with factors of dose and time (within session) were conducted to examine time course within sessions and 2) one-factor, repeated measures analyses of variance to test the main effect of dose using the sum across time points. Complete time course data for pupil diameter were not obtained on Subjects 1 and 2; therefore, the time course analyses for pupil diameter included two fewer subjects than the single time point analyses. Changes from predrug baseline ratings of individual items in the adjective rating scales were summed across session time for each dose condition tested in the generalization phase and analyzed using one-factor, repeated measures analyses of variance to test the main effect of dose for each drug. Conservative F-tests employing Huynh-Feldt probability levels were used to interpret the results of all analyses of variance. Effects were considered statistically significant if $p<0.05$.

RESULTS

Effects of Training Drugs

The effects of the three training drugs were compared by analyzing the data from the training and test of acquisition sessions

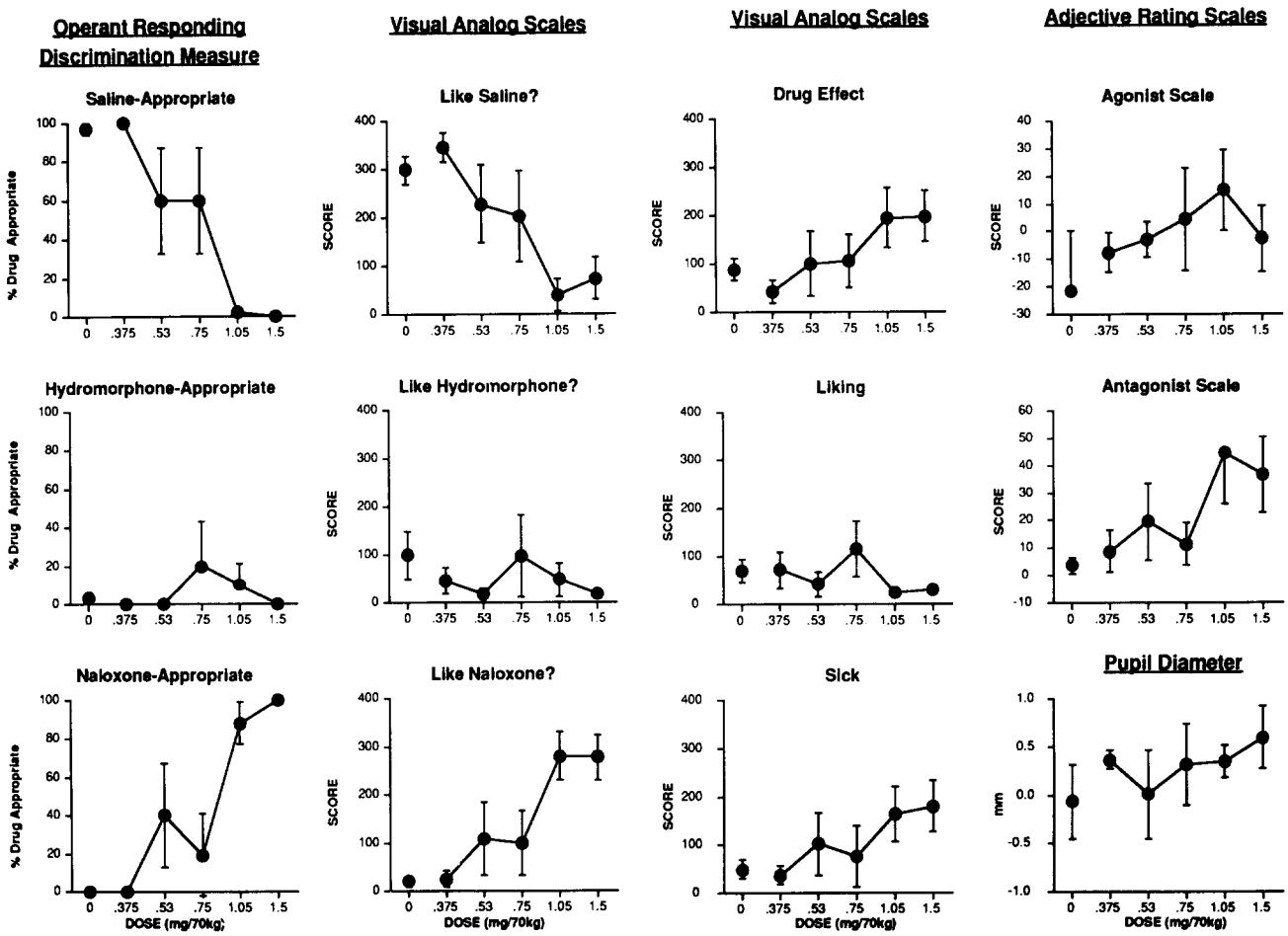

FIG. 3. Dose-response curves of selected measures produced by test doses of butorphanol and saline in opioid-dependent subjects trained to discriminate between hydromorphone 10 mg/70 kg, saline 2.0 ml, and naloxone 0.15 mg/70 kg. See Fig. 1 caption for details.

(sessions 1–12; sessions 7–12 for the discrimination measures). A portion of the data for the first subject were lost due to computer malfunctions; therefore, for consistency, all data from this subject was omitted from these analyses.

The discrimination between the three training drugs was readily learned, and few errors were made in identifying the training doses during the test of acquisition sessions (7–12). Hydromorphone 10.0 mg and naloxone 0.15 mg were correctly identified in 100% of occasions in all three discrimination components (Table 2). Saline 2.0 ml was less reliably identified (87% correct), with similar results for each of the three discrimination measures. On the occasion that an error was made, saline was incorrectly identified as hydromorphone.

Significant treatment effects were produced on each of the nine quantitative visual analog scales; hydromorphone and naloxone were rated significantly higher than placebo on the "any drug effects" (strength) scale (Table 2). Hydromorphone also produced a significantly greater "liking" and "high" scale scores than either saline or naloxone and significantly greater "good effects" scores than naloxone while subjects reported significantly greater "bad effects" and "sick" for naloxone than for saline or hydromorphone. On the visual analog scales on which subjects rated "How much does this drug feel like . . . ?" each drug was rated as being significantly more similar to itself than was either of the other training drugs.

On the adjective rating scales only the Antagonist scale showed significant treatment effects, with naloxone producing a significantly higher score than either saline or hydromorphone. Analyses of the individual items in the scale indicated that naloxone significantly increased ratings of the following individual items: flushing, sweating, runny nose, chills, shaky, tired, gooseflesh, restless, and agitated. Hydromorphone had no significant effects on any of the adjective rating scales, although it did produce some nonsignificant elevation of the Agonist scale score.

On the ARCI only the PCAG scale showed a significant treatment effect, with naloxone producing a significantly higher score than either saline or hydromorphone. Also, naloxone produced substantial but nonsignificant decreases in the MBG scale score and increases in the LSD scale score. Hydromorphone produced only small, nonsignificant effects.

Effects of the training drugs on physiological parameters were slight. Only pupil diameter showed a significant treatment effect, with hydromorphone producing a significant constriction and naloxone producing a significant dilation relative to saline.

No significant drug effects on DSST psychomotor performance were observed, although there was a nonsignificant trend for poorer performance following naloxone.

Results of the drug class identification questionnaire are shown

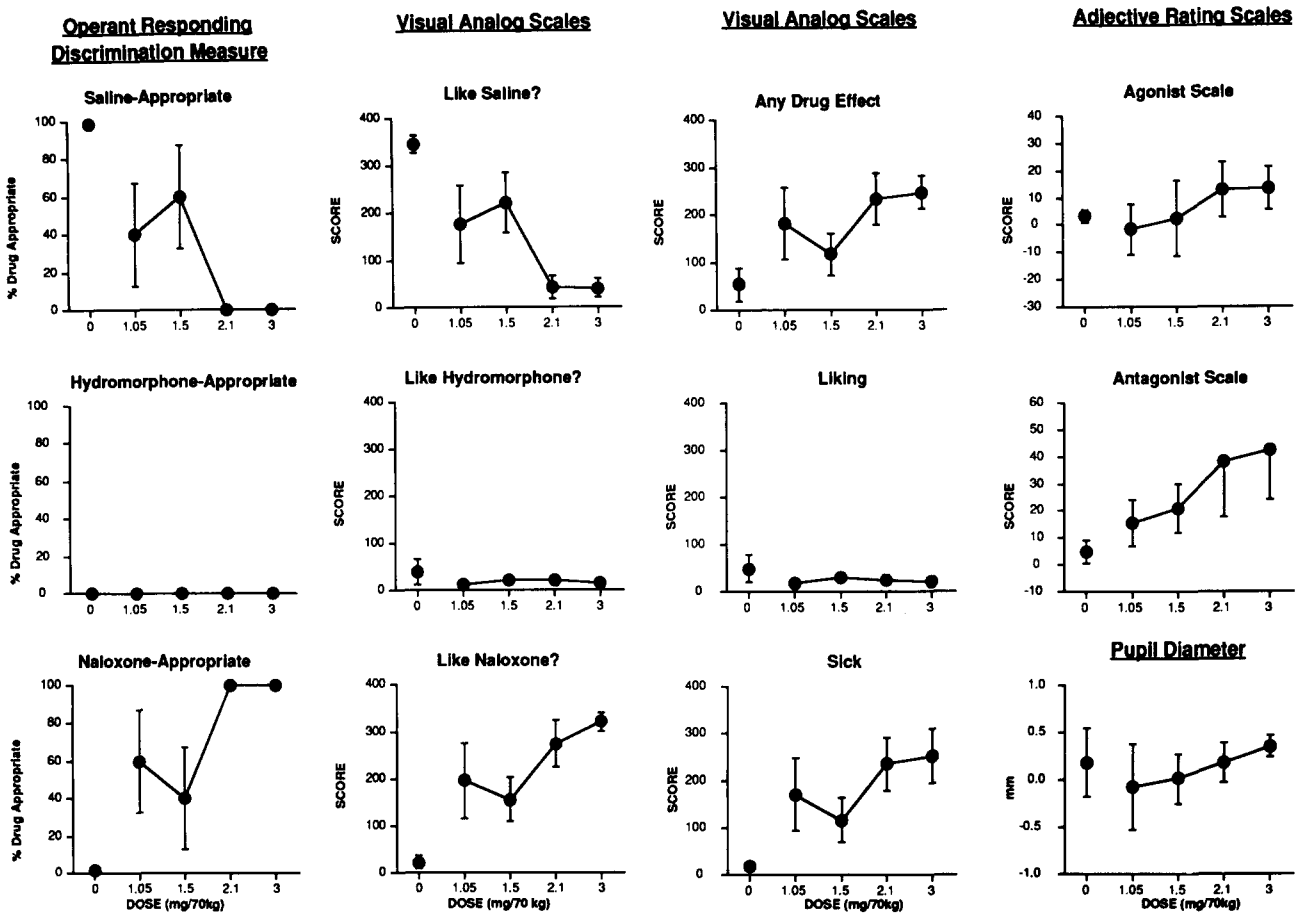

FIG. 4. Dose-response curves of selected measures produced by test doses of nalbuphine and saline in opioid-dependent subjects trained to discriminate between hydromorphone 10 mg/70 kg, saline 2.0 ml, and naloxone 0.15 mg/70 kg. See Fig. 1 caption for details.

in Table 3. Saline was identified as a placebo in 93.8% of responses; hydromorphone was identified as an opiate in 93.8% of responses; and naloxone was identified as an opioid antagonist in 100% of responses.

Generalization Testing

Analyses of the within-session time courses of the effects of each of the test drugs across the session showed very little effect. Therefore, data for discrimination measures are presented as mean across the two observations in each session, and data for subjective and physiological measures are presented as the sum of scores or change from baseline scores across the four observations in each session. Results of the generalization testing are summarized in Table 4, and selected variables are shown in Figs. 1–4. Table 4 presents p values for measures for which p values less than or equal to 0.06 were determined in the analyses of variance; the directions of drug effects relative to saline are indicated by arrows. As in the training and test of acquisition sessions similar results were found on all three discrimination measures; only the results from the operant response discrimination measure are shown in the graphs. Typically, individual subjects made 100% of their responses to a single discrimination alternative during each session for each generalization drug.

On the discrimination measures hydromorphone (Fig. 1; Table 4) produced dose-related increases in identifications as hydromorphone and dose-related decreases in identifications as saline. Hydromorphone at doses of 3.5 mg and greater was identified as hydromorphone in 80% to 100% of trials. Hydromorphone was never identified as naloxone. On the visual analog scales measuring the similarity of the test drug to each of the training drugs hydromorphone produced dose-related increases in ratings of similarity to hydromorphone 10 mg and decreases in ratings of similarity to saline. As in the behavioral discrimination measures, hydromorphone was subjectively rated as being not at all similar to naloxone. Hydromorphone produced significant increases in the "Any Drug Effect," "High," "Liking," and "Good Effects" visual analog scales. In the adjective rating scale, hydromorphone produced increases in the Agonist adjective rating scale though this effect was not statistically significant. In analyses of individual adjective scale items, hydromorphone significantly increased ratings only on the Sleepy adjective item. Hydromorphone had no significant effects on any of the ARCI scales. On the pharmacological class questionnaire (Table 5) hydromorphone produced dose-related increases in identifications as an opioid with 10 mg being identified as an opioid in 100% of opportunities, and doses of 3.5 mg or greater being identified as an opioid on 80% or more of opportunities.

TABLE 5

RESULTS OF THE PHARMACOLOGICAL CLASS IDENTIFICATION QUESTIONNAIRE

	Placebo	Opioid	Opioid Antagonist	Barbiturate/ Benzodiazepine	Antidepressant	Stimulant
Hydromorphone (mg/70 kg)						
0	95	5	—	—	—	—
2.5	40	40	—	20	—	—
3.5	20	80	—	—	—	—
5.0	5	95	—	—	—	—
7.0	20	80	—	—	—	—
10.0	—	100	—	—	—	—
Naloxone (mg/70 kg)						
0	100	—	—	—	—	—
0.375	55	—	45	—	—	—
0.053	70	—	25	5	—	—
0.075	5	—	80	10	5	—
0.105	—	—	100	—	—	—
0.15	—	—	100	—	—	—
Butorphanol (mg/70 kg)						
0	85	15	—	—	—	—
0.375	100	—	—	—	—	—
0.53	65	—	35	—	—	—
0.75	60	20	20	—	—	—
1.05	5	—	85	5	—	5
1.50	10	—	85	5	—	—
Nalbuphine (mg/70 kg)						
0	100	—	—	—	—	—
1.05	40	—	60	—	—	—
1.5	50	—	50	—	—	—
2.1	5	—	95	—	—	—
3.0	5	—	95	—	—	—

Values represent percent of occasions subjects identified each drug condition as each pharmacological class. Data were collected four times in each session; each drug condition was tested once in each of five subjects. Barbiturate and benzodiazepine identifications were combined. No responses were given for other drug classes listed on the questionnaire.

Naloxone (Fig. 2; Table 4) produced dose-related increases in identifications as naloxone and dose-related decreases in identifications as saline. Naloxone doses of 0.075 mg and higher were discriminated as naloxone in greater than 80% of opportunities. Naloxone produced no identifications as hydromorphone. On the visual analog scales measuring the similarity of the test drug to each of the training drugs naloxone produced dose-related increases in ratings of similarity to naloxone 0.15 mg and dose-related decreases in ratings of similarity to saline. Naloxone produced significant increases in the "Any Drug Effect," "Bad Effects," and "Sick" visual analog scales. Naloxone significantly increased ratings on the Antagonist and Mixed Agonist-Antagonist adjective rating scales and on the following individual items: flushing, sweating, heavy or sluggish feeling, watery eyes, runny nose, chills, tired, and depressed. Naloxone also produced increases in the PCAG scale and decreases in the MBG scale of the ARCI. On the pharmacological class questionnaire (Table 5) naloxone was identified as an opioid antagonist with 0.105 and 0.15 mg being identified as an antagonist in 100% of opportunities, and 0.075 in 80% of opportunities.

Butorphanol (Fig. 3; Table 4) produced dose-related increases in identifications as naloxone and dose-related decreases in identifications as saline. There was complete generalization of butorphanol 1.5 mg to naloxone with 100% naloxone-appropriate responses. On the visual analog scales measuring the similarity of the test drug to each of the training drugs butorphanol produced dose-related increases in ratings of similarity to naloxone 0.15 mg and decreases in ratings of similarity to saline. Butorphanol produced significant increases in the "Any Drug Effect," "Bad Effects," and "Sick" visual analog scales. Butorphanol produced significant increases in the Antagonist adjective rating scale scores and flushing and chills, individual items on the adjective rating scale. Butorphanol had no significant effects on any of the ARCI scales. On the pharmacological class questionnaire (Table 5) butorphanol produced dose-related increases in identifications as an opioid antagonist, with the two highest doses (1.05 and 1.50 mg) being so identified on 85% of opportunities.

Nalbuphine (Fig. 4; Table 4) produced dose-related increases in identifications as naloxone and dose-related decreases in identifications as saline. There was complete generalization of nalbuphine 2.1 and 3 mg to naloxone with 100% naloxone-appropriate responses. On the visual analog scales measuring the similarity of

the test drug to each of the training drugs nalbuphine produced dose-related increases in ratings of similarity to naloxone 0.15 mg and dose-related decreases in ratings of similarity to saline. Nalbuphine produced significant increases in the "Any Drug Effect," "Bad Effects," and "Sick" visual analog scales. Nalbuphine had significantly increased scores on the Mixed Agonist-Antagonist adjective rating scales and on turning of stomach, drive, chills and shaky, individual items on the adjective rating scale. Nalbuphine had no significant effects on any of the ARCI scales. On the pharmacological class questionnaire (Table 5) nalbuphine produced dose-related increases in identifications as an opioid antagonist, with the two highest doses (2.1 and 3 mg) being so identified on 95% of opportunities.

None of the drugs had significant effects on any of the physiological measures. Hydromorphone alone produced a small, but statistically significant, effect on DSST performance; however, the change in the number of trials attempted was not dose related.

In order to determine whether identification of a test drug as a particular training drug was associated with identification of the drug as a particular pharmacological class, the data from cycles three and four in which both the discrimination measures and the pharmacological class questionnaires were collected were summarized; both time points for all doses of each drug tested were combined. In general, the identifications on the subjective pharmacological class questionnaire agreed closely with the behavioral drug discrimination performance. Whenever subjects discriminated a test drug as saline in the behavioral discrimination measure, they identified it as a blank (placebo) on the pharmacological class questionnaire in 97% of occasions (across all test drugs and saline). Similarly, whenever subjects discriminated a test drug as hydromorphone in the behavioral discrimination measure, they identified it as an opiate on the pharmacological class questionnaire in 98% of occasions (across all test drugs and saline). Drugs discriminated as naloxone in the behavioral discrimination measure were identified as an opioid antagonist in 100% of opportunities.

In a previous study butorphanol was found to precipitate a somewhat different withdrawal syndrome than that of naloxone in methadone-dependent subjects (16). Specifically, butorphanol produced significantly less lacrimation and rhinorrhea than naloxone. In a similar study no significant differences between nalbuphine- and naloxone-precipitated withdrawal were found (18). To determine whether these findings were replicated in the present study two-factor analyses of variance (drug condition and dose) were conducted on the sum of change from baseline of the adjective rating scale scores and individual items scores for naloxone 0.075, 0.105, and 0.15 mg, butorphanol 0.75, 1.05, and 1.5 mg, and nalbuphine 1.5, 2.1, and 3 mg. There were no significant differences between butorphanol and nalbuphine on any items or scale scores. Nor were there significant differences between naloxone and either butorphanol or nalbuphine on the Withdrawal, Agonist, or Mixed Agonist-Antagonist scale scores, indicating that overall the magnitudes of effects of the three drugs at the doses compared were similar. However, ratings on the individual items watery eyes, runny nose, and tired following butorphanol administration were significantly less than those produced by naloxone. Nalbuphine also produced significantly lower ratings of watery eyes than naloxone.

DISCUSSION

The present study provides further information about the discriminative stimulus and subjective effects of the opioid mixed agonist-antagonists butorphanol and nalbuphine, about the relationship between discriminative stimulus effects and subjective effects, and about the dependence of the quality of these effects upon the specific experimental procedures used.

The present study replicated the results of our initial hydromorphone-naloxone-saline discrimination study in dependent subjects (14) and, in addition, tested the effects of two mixed agonist-antagonists, butorphanol and nalbuphine. Both butorphanol and nalbuphine generalized to naloxone and produced profiles of subjective effects similar to those produced by naloxone in subjects physically dependent on methadone 30 mg/day. Neither butorphanol nor nalbuphine consistently generalized to hydromorphone; thus, neither of these agonist-antagonists produced discernable agonist effects at any dose tested in subjects maintained on low levels of opioid physical dependence.

There was a general similarity of withdrawal syndromes produced by butorphanol, nalbuphine and naloxone though the syndromes were not identical. Naloxone, butorphanol and nalbuphine increased naloxone-appropriate responding, ratings on the Drug Effects, Bad Effects and Sick visual analog scales and were frequently identified as opioid antagonists. However, on individual withdrawal symptoms, butorphanol produced less watery eyes, runny nose and tired, and nalbuphine produced less watery eyes than naloxone. The present study replicated the results of an acute effects study in which butorphanol was found to produce significantly less watery eyes, runny nose, and yawning than naloxone (16). Nalbuphine, on the other hand, produced a withdrawal profile indistinguishable from that of naloxone in an acute effects study (18). Results of the present discrimination study indicate that, overall, both butorphanol and nalbuphine produced precipitated withdrawal that was naloxone-like, but also support the findings of some differences between butorphanol-, nalbuphine-, and naloxone-precipitated withdrawal on the subjective measures. Thus, different compounds sharing a general opioid antagonist activity may have subtly different profiles of withdrawal signs and symptoms. Further drug discrimination studies may be useful to determine whether subjects can be trained to discriminate the differences between these withdrawal syndromes.

The relatively greater antagonist activity of nalbuphine compared to butorphanol suggested by the animal literature was demonstrated in the present study. The recommended therapeutic doses of butorphanol and nalbuphine are 2 mg and 10 mg, respectively, and are approximately equivalent to 10 mg of morphine in producing analgesia and respiratory depression (6). Using the criterion of 80% naloxone-identifications as an index of antagonist activity, nalbuphine is a potent antagonist relative to its agonist effects, producing precipitated withdrawal at 2.1 mg, approximately one-fifth the analgesic dose (10 mg). Butorphanol produced precipitated withdrawal at 1.05 mg, approximately one-half the analgesic dose (2 mg). Using the antagonist/agonist dose ratio, both nalbuphine and butorphanol appear to have greater antagonist activity than another marketed agonist-antagonist buprenorphine. Therapeutic doses of buprenorphine (0.2 and 0.3 mg) failed to precipitate withdrawal in subjects maintained on methadone 50 mg/day PO (17), making its antagonist/agonist dose ratio greater than one.

The present study replicates the findings of the above-mentioned studies that both butorphanol and nalbuphine precipitate withdrawal in methadone-dependent humans. While nalbuphine's antagonist actions such as precipitating withdrawal in morphine-dependent subjects have been well documented (8,19), butorphanol has been reported not to precipitate withdrawal in morphine-dependent rhesus monkeys and humans (3,7,20). Perhaps the precipitation of withdrawal by butorphanol in our studies is related to our use of methadone as the dependence-sustaining agonist.

The present study's concurrent assessment of multiple indices

permits comparison of the relative sensitivity of the behavioral discrimination measures, visual analog scales, adjective rating scales, and ARCI scales. The computerized assessment instrumentation used in this study is an important technological feature that has permitted the convenient collection of multiple subjective effect measures and their comparison with one another and with the behavioral discrimination measures. Such data are very cumbersome to handle in paper-and-pencil format. The behavioral discrimination measures and visual analog scales showed the greatest degree of sensitivity to the dose effects of the administered drugs. This is apparent in the consistency with which significant effects were observed with these measures and in the high degree of statistical significance achieved. The statistical probability levels (p-values) obtained with the discrimination measures and visual analog scales were commonly 10- to 100-fold greater than those obtained with the adjective rating and ARCI scales that attained significance. It is especially noteworthy that the ARCI scales proved relatively insensitive since they are widely viewed as the standard instruments for assessing subjective effects of drugs of abuse. The differences in observed sensitivity may be related to differences in question content, to differences in response scaling (ARCI responses are dichotomous true/false), or to other factors.

The categorization of drugs in the drug discrimination procedures was dependent upon the specifics of the drug discrimination procedure. In other studies we have shown nalbuphine and butorphanol to be discriminated as being similar to hydromorphone or pentazocine (15). Certainly their present discrimination as naloxone-like is dependent on the subjects' being physically dependent. The dose-effect functions obtained in the present study, when compared to those obtained in other studies using nondependent volunteers, reveal the effect of opioid tolerance and dependence (in this case, methadone maintenance) on subjects' sensitivity to the effects of opioid agonists and antagonists. In prior work with nondependent postaddicts (15) a hydromorphone dose of 2 mg/70 kg both produced subjective effects and was correctly discriminated. In the present study a hydromorphone dose of 3.5 mg/70 kg was needed. This represents a two-fold shift of the dose-effect function to the right—to reduced opioid sensitivity in methadone-treated subjects. Presumably this induced opioid tolerance is one of the mechanisms contributing to the therapeutic efficacy of methadone maintenance treatment of opioid addiction. Conversely, sensitivity to naloxone is dramatically increased in methadone-treated subjects. Doses as low as 0.075 mg/70 kg produced both subjective and discriminative effects in the present study. In nondependent subjects, doses greater than 100 mg can be given with minimal effect (1,11).

The drug discrimination procedure has been shown to be valuable for assessing and characterizing multiple effects of psychopharmacological agents. It is compatible with concurrently collecting a broad array of discrimination, subjective and physiological measures providing the opportunity to describe the effects and the relative similarity of novel drugs to standard drugs under a variety of conditions (for example, in nondependent and opioid-dependent subjects or using different training drugs). This procedure will be useful in studying opioid-receptor pharmacology and in assessing the abuse liability of new opioids.

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