Pharmacology Biochemistry & Behavior, Vol. 30, pp. 967–975. Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

The Psychopharmacologic and Prolactin Response After Large Doses of Naloxone in Man

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Received 27 July 1987

KUMOR, K. M., C. A. HAERTZEN, D. R. JASINSKI AND R. E. JOHNSON. *The psychopharmacologic and prolactin response after large doses of naloxone in man.* PHARMACOL BIOCHEM BEHAV **30**(4) 967–975, 1988.—Large doses of naloxone (150–300 mg), placebo, and morphine (15–30 mg) were given intramuscularly to human volunteers and compared using measures of subjective feeling states, physiological measures and discriminative features. Plasma prolactin responses after naloxone 210 mg and placebo were compared. The subjective measures and discriminative features of naloxone revealed that the drug is subtly psychoactive but the stimulus is vague and cannot be identified clearly as an opioid agonist or antagonist in nondependent opioid-using volunteers. The physiologic and prolactin responses closely resembled opiate agonist activity. We conclude that naloxone in this dose range may act as an opiate agonist in man.

Naloxone Opioid Opiates Subjective effects Psychopharmacology Prolactin Withdrawal Agonist-antagonist Human

THE opioid antagonist, naloxone, is a drug with fundamental importance as a tool for research into opioid receptor-mediated mechanisms. Blockade by naloxone has become the sine qua non for defining a drug action as opiate in nature [17,31].

It is accepted that there exists more than one kind of opioid receptor and that naloxone is effective in blocking the actions of drugs at these different opioid receptors [11, 17, 25]. However, the dose of naloxone necessary to effectively block subclasses of receptors differs widely [16, 22, 25]. This phenomenon has been used in two ways to investigate the action of opioids. Dose-response curves of the activity of antagonists in combination with agonists have been used to demonstrate the presence of multiple opioid receptors in pharmacological and behavioral experimental work [6, 13, 22]. Alternatively differential sensitivity to naloxone has been used to separate the activities of certain opioid subclasses. This is achieved by blocking the activity of the more sensitive opioid receptor in order to study the activity of the less sensitive receptor [32]. These research approaches rely on the assumption that naloxone, given alone, in the dose ranges studied, is without significant activity on the assay system employed.

Jasinski *et al.* [18] studied naloxone doses up to 24 mg/70 kg (approximately 0.34 mg/kg) in man and found that naloxone acted as an opiate antagonist. Several studies report subtle psychoactivity after naloxone is administered to nondependent opiate using human volunteers in doses of 3 mg/70 kg to 280 mg/70 kg (approximately 0.43 mg/kg to 4.0 mg/kg) [3, 12, 19, 20]. Other studies have also reported changes in vital signs after naloxone [12, 34, 37]. Although some investigators suggest that the actions of naloxone are due to blockade of the effects of endogenous opiates, this remains unproven [3, 4, 12].

Similarly some behavioral studies of animals have shown that naloxone can alter certain complex behaviors and have concluded that the activity of naloxone was acting as an opiate antagonist [28,29]. However, the work of other investigators studying human volunteers or animals has suggested that large doses of naloxone have opiate agonist activity [1, 9, 23, 24, 37]. The purpose of this study was to characterize the pattern of pharmacologic responses to naloxone 300 mg as those of an opioid agonist, agonist-antagonist or antagonist. Although Cohen *et al.* [3,4] and Jones and Herning [19] have studied the effects of large doses of naloxone in man, they did not use scales which were designed to measure morphine-like effects such as the Addiction Research Center Inventory [14], the Single Dose Questionnaire [10], the Feel the Drug Questionnaire or the Drug Similarity Rating [21]. Furthermore, the Addiction Research Center Inventory also includes several scales which measure withdrawal. These scales and the hormone prolactin response were used to define the activity of naloxone in this dose range as opiate agonist or antagonist in man. The prolactin response was used because prolactin increases after a morphine challenge but is unchanged in withdrawal [2, 8, 26, 33]. The profile of activity of large doses of naloxone has importance for designing experiments in which

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naloxone is used for blockade or selected opioid receptor subclasses in human research.

METHOD

Two experiments were done. The first compared the subjective and physiologic effects of naloxone, morphine and placebo. The second experiment measured the changes in the prolactin concentration in response to naloxone.

Subject Population

The criteria for paid volunteer subjects admitted for either experimental study included a history of illicit use of both opioid and hallucinogenic substances. The screening procedures for acceptance of the subjects required that they pass physical examinations, scored within the norm on the Shipley Institute of Living Scale and the Symptom Check List-90 aggression scale, and could demonstrate an understanding of the consent form. All subjects were observed and scored using the Himmelsbach scoring system for rating the intensity of withdrawal three times daily for a period of 3 days prior to study in order to screen out physically dependent opioid users [15]. Mean scores and ranges of the daily Himmelsbach scale for these three days were: 1st day 3 (0–13), 2nd day 0.75 (0–3), and 3rd day 0.75 (0–3). These scores are very low and indicate a lack of opioid dependence [15].

Fourteen male subjects (10 for experiment I and 7 for experiment II), aged 21–35, meeting these criteria were recruited using word of mouth, newspaper advertisements and circulation of fliers. Subjects were housed on a closed unit to prevent illicit drug use. Random urine screens measuring drugs of abuse were used to document that the subjects refrained from drug use while participating in the experiment.

EXPERIMENT I

Drug Doses

The drug conditions and test doses administered were morphine 15 and 30 mg, naloxone 150 and 300 mg and placebo. Training doses were given prior to these test doses for the purpose of making measurements of drug discrimination. The training doses were morphine 21 mg, ketocyclazocine 0.85 mg, cyclazocine 0.7 mg, naloxone 210 mg and placebo. Both training doses and test doses were administered via a two ml intramuscular injection into the buttocks on an every third or fourth day schedule.

Measures

The assessment battery included physiologic measurements, subjective rating scales and identification and discrimination judgements. We measured standing and supine blood pressures and pulses, rectal temperature, respirations and pupil diameter. We scaled psychopharmacologic activity using subjective and objective questionnaires. These included the Single Dose Questionnaire for subjects and observers [10], the full Addiction Research Center Inventory (ARCI) and its subscales, the Morphine Benzedrine Group (MBG), the LSD Group (LSD), and Pentobarbital, Alcohol and Chlorpromazine Group (PCAG) subscales [14], an interval scale of drug liking, and the Perception Scale [21]. Except for the ARCI, these scales were given on the same schedule as the physiologic measures. The full ARCI was given once each study day at one hour postdrug administration. We also employed a drug identification-matching procedure and the Drug Similarity Rating Scale (DSR) which were given at 24 hr after drug administration [21].

The Perception Scale is an interval scale (integers 0–9) of forty questions which was developed by us previously to reflect subjective alterations in the five senses as well as cognition, feelings of detachment, paranoia and general mood [21]. The questionnaire is scored as the sum of numerical responses. It is also broken down into subscales named for the sense or mental process the questions probe. Some questions are assigned into more than one subscale and the response to these are summed separately into each subscale.

The battery of subjective and observer rating scales and physiologic measures was given at −60, −30, +15, +30 minutes and 1, 2, 3, 4, 5, 8 and 12 hours after an intramuscular dose administration. The volume of the naloxone concentrated solution necessitated that two 2 ml injections be given at the same time into deltoid or quadriceps muscles.

The drug administration procedure involved a task of matching an unidentified drug (test drug) with a drug from the set of training drugs which were presented to the subject as a series of doses administered prior to the test doses. The training doses were only identified to the subject as drugs A, B, C, D, or E [21]. Subjects wrote notes about drug effects after each training dose for their subsequent reference. Subjects were not paid for correct identification nor were they told until after the study completion the results of their identification. This rating was done on the morning after study days.

The Drug Similarity Rating scale required the subject to answer 5 questions relating how similar the unknown (test) drug was to each of the training doses, A, B, C, D, or E [21]. The rating was a 0–4 interval scale with 0 identified as not-at-all, 1 as slightly, 2 as moderately, 3 as very much and 4 as exactly. This measure was done on the morning after study days.

Design and Analysis

For the physiologic, psychopharmacologic and drug discrimination measurements, ten subjects were studied in a randomized double-blind design. Statistical differences were determined by analysis of variance of the time averaged mean measurements of physiological variables or scale scores of the drug conditions. The data were analyzed as the time-weighted mean measurement between 15 min and 5 hr. The time-weighted mean measurement is an expression of the area under the curve of the response versus time. The major independent factors for the analysis of each measure were drug conditions and the subjects. For one of the measures, the MBG group scale, the baseline measurements preceding drug administration differed significantly among the drug conditions in that the placebo baseline differed from the other test day baselines. For this measure the baseline measurements for all the drug conditions were subtracted from the measurements after drug administration. The resultant data were then analyzed using analysis of variance techniques as described for the other measures.

The drug similarity rating scores were used to derive a scalar measure of the difference between any two drugs or doses. This was done as previously described [21], using a discriminative analysis procedure in which a sum of "t-squares" is calculated for a pair of drug conditions from the scores on each of the five rating questions. The square root of this sum is the scalar quantity which is the difference between a pair of drugs. This process was repeated for each drug pair so that the relationships of the drugs to each other may be presented as a dimensional figure.

TABLE 1

PHYSIOLOGIC MEASUREMENTS MEAN TIME-WEIGHTED MEASUREMENT OVER 5 HOURS (N=10)

Measure	Placebo	Morphine (15 mg)	Morphine (30 mg)	Naloxone (150 mg)	Naloxone (300 mg)	Significant Difference	p value
St Sys BP	109	116*	116*	114*	116*	3.7	0.015
St Dias BP	76	79	80	80	79	NS	0.46
Sup Sys BP	113	113	119*	115	116	3.3	0.017
Sup Dias BP	69	72	73	70	71	NS	0.07
St Pulse	85	85	90	85	85	NS	0.09
Sup Pulse	71	72	78*	73	72	3.5	0.043
Temperature	36.03	35.77*	35.73*	35.84*	35.86*	0.16	0.021
Respiration	19	18	17	18	18	NS	0.08
Pupil Size	4.8	3.5*	3.1*	4.9	4.8	0.24	2.5×10^{-17}

*Significantly different from placebo, one-tailed, $p<0.05$.

The scores of the ARCI were treated in a similar fashion as the drug discrimination data described in the previous paragraphs in order to measure the magnitude of the differences between the drugs using an established measure with a standard frame of reference [21].

EXPERIMENT II

Seven subjects (3 participated in Experiment I) participated in the prolactin measurements which were conducted in a double-blind, crossover design. Plasma samples were obtained after intramuscular injection of naloxone 210 mg and placebo on two study days spaced at least 2 days apart. Blood was taken through an indwelling catheter at 30 min prior to drug administration and at 15 min, 30, min, 1 hr, 2 hr, 3 hr, 4 hr, and 5 hr after drug administration. No questionnaires were administered on these days. Prolactin was assayed with commercial kits by standard techniques as described previously [5]. Statistical differences were determined by two way analysis of variance of the drug conditions (naloxone and placebo) and time (−30 to 300 minutes).

RESULTS

Experiment I

Naloxone was differentiated from placebo on some of the psychopharmacologic and physiologic measures. The time course of the activity of naloxone was similar to morphine. The best measures of naloxone activity were the "Feel Drug" scale and the rectal temperature because they differed significantly from placebo at both the higher and lower doses and had low coefficients of variation allowing interpretation of the time course. The peak of naloxone activity occurred between one to two hours for the "Feel Drug" scale scores and between two to three hours for the minimum body temperatures. The duration of action was 3 to 4 hours as measured by the "Feel Drug" scale and at least 5 hours as measured by the rectal temperatures. (Fig. 1A and B).

Physiologic measures. Naloxone 150 mg and 300 mg caused an increase in the standing systolic blood pressure as compared to placebo (Table 1). There was no significant change in the standing diastolic and supine blood pressures, as compared with placebo. Naloxone 150 mg and 300 mg caused a decrease in the body temperature as compared to placebo. There was no effect of naloxone on the pulse or pupil diameter but there was a strong trend toward signifi-

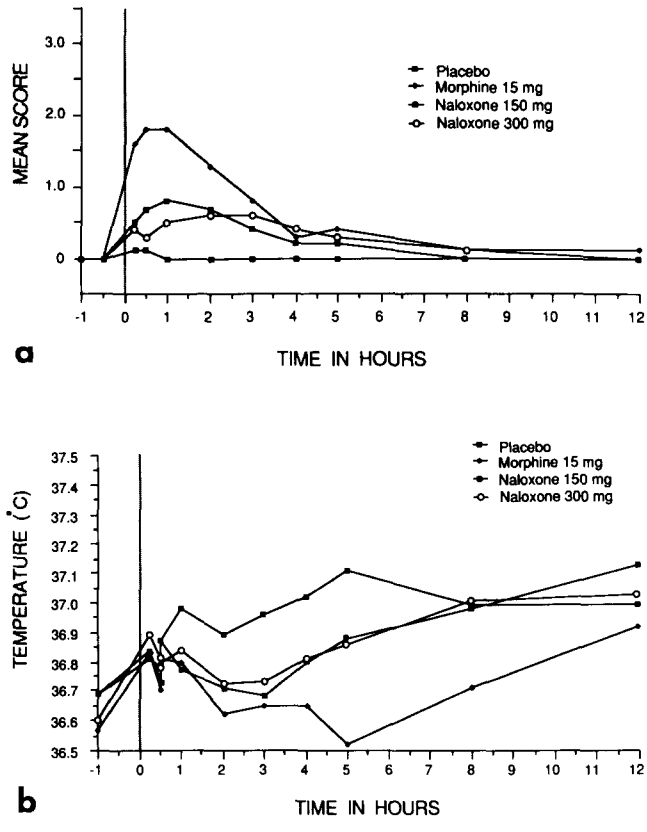

FIG. 1. (a) The mean "Feel the Drug" scale scores plotted versus time for 10 subjects. The scale is scored 0 for "not at all," 1 for "slight," 2 for "moderate" and 3 for "alot." The vertical line at time zero indicates the time of the intramuscular injection of drug. (b) The mean rectal temperatures plotted versus time. The vertical line at time zero indicates the time of the intramuscular injection of drug.

TABLE 2

QUESTIONNAIRES FOR SUBJECTS AND OBSERVERS
MEAN TIME-WEIGHTED SCORES OVER 5 HOURS (N=10)

Scale	Placebo	Morphine (15 mg)	Morphine (30 mg)	Naloxone (150 mg)	Naloxone (300 mg)	Significant Difference	p value
Subject Ratings							
Feel Drug	0.1	5*	10*	2.4*	2.3*	2.1	2.2×10^{-8}
Liking	1	7.3*	8.4*	.0	0.6	3.4	8.1×10^{-5}
MBG	14.7	29.8*	33.3*	9.8	12.2	11.5	2.5×10^{-3}
PCAG	15.3	20.8	22	23.2	19.3	NS	0.09
LSD	16.1	17	17.7	22	18.5	NS	0.13
Observer Ratings							
Liking	0	3.8*	7.3*	0	0.17	2.4	6.5×10^{-6}
Drug Effect	0.1	2.3*	4.4*	0.7	1.1*	0.9	2.1×10^{-8}
Normal	4.8	2.5*	0.5*	4.2	3.8*	0.94	1.8×10^{-8}

*Same as Table 1.

TABLE 3

PERCEPTION SCALE MEAN TIME-WEIGHTED SCORES OVER 5 HOURS (N=10)

Scale	Placebo	Morphine (15 mg)	Morphine (30 mg)	Naloxone (150 mg)	Naloxone (300 mg)	Significant Difference	p value
Global	13.7	45.7*	60.2*	42*	28.3	25.9	4.2×10^{-2}
General	5.5	19.2	31.7*	19.8*	11.7	14.3	4.0×10^{-2}
Detachment	0.7	8.5*	16.4*	7.4	2.9	7.0	5.9×10^{-3}
Visual	0.9	0.8	1.1	1.4	1	NS	0.42
Auditory	4.6	7.1	6.4	6.8	5.4	NS	0.14
Tactile	1.2	13.7*	14.3*	2.9	1.2	10.0	5.8×10^{-2}
Taste	2.3	9.6	15.7	9.6	12.3	NS	0.33
Smell	0	0	0	0	1.5	NS	0.42
Dizziness	0.1	0.5	0.4	0.1	0	NS	0.4
Cognitive	2	4.3	4.6	5.4	3	NS	0.44
Paranoia	0	0	0	0.1	0	NS	0.42

*Same as Table 1.

cance for respiratory rate depression ($p<0.08$) though the magnitude of the changes were small. The analysis of variance for respiratory rate and the standing diastolic blood pressure indicated that the intersubject variation contributed more to the total sample variation than did the drug conditions. The differences among the subjects for these two measures was significant ($p<0.01$). Morphine, 15 mg and 30 mg, differed from placebo in its effects on the standing systolic blood pressure, temperature and pupil size. There was also an increase in the supine systolic blood pressure and pulse after 30 mg of morphine. The standing diastolic blood pressure and respiratory rate after morphine trended toward significant changes from placebo.

Psychopharmacologic measures. Naloxone demonstrated only slight activity on the scales measuring feelings and mood states. The effects of both doses of naloxone, 150 mg and 300 mg, differed significantly from placebo on the "Feel Drug" scale (Table 2). However, these responses were not dose dependent. Naloxone scores did not differ from placebo scores on the MBG, PCAG, and LSD subscales of the ARCI. The PCAG score exhibited a trend toward an increase after naloxone. There was no detectable change in the scores on the Liking scale for naloxone compared to placebo. The 150 mg dose of naloxone did differ significantly from placebo on the Global Perception scale scores (Table 3). The average hourly score for this dose of naloxone of 42 was similar to the score of 47.5 after 15 mg of morphine. Scores on several subscales of the Perception Scale accounted for the activity on the Global Perception Scale score which is a summed score for all the questions on the scale. The scores after the 150 mg dose of naloxone on the General and Detachment subscales demonstrate increases from those after placebo although only the General scale scores reached a statistically significant level ($p<0.04$) while the Detachment scale scores narrowly missed significance. Like the Full Perception Scale scores, the scores for the lower naloxone dose on the General and Detachment subscales were similar to the scores for the low morphine dose (15 mg). Examination of the raw data revealed that the scores of four individuals contributed substantially to the significant results. The scores of these four individuals who made large contributions to the lower naloxone dose scores showed that each of these persons had scored the 300 mg naloxone dose much lower than the 150 mg dose. The 300 mg

TABLE 4

OPIATE SYMPTOMS SCALES MEAN TIME-WEIGHTED SCORES OVER 5 HOURS (N=10)

Symptoms	Placebo	Morphine (15 mg)	Morphine (30 mg)	Naloxone (150 mg)	Naloxone (300 mg)	Significant Difference	p value
Whole	2.6	12.3*	19.9*	5.8	4.3	5.4	1.9×10^{-5}
High	0.1	2.3*	3.4*	0.9	0.1	1	1.8×10^{-6}
Yawning	0	0	0.1	0.2	0.9*	0.5	2.7×10^{-2}
Coasting	0.1	0.8	1.2	0	0	NS	0.1
Sleepy	0.1	0.9	1.4	1.3	0.5	NS	0.06
Turning Stom	0.1	1.2	1.7	0.7	0.9	NS	0.18
Pleasant sick	0	0.9	1	0	0.2	NS	7.8×10^{-2}
Drive	0	0.1	0.7	0	0	NS	0.18
Soap box	0	0.3	1*	0	0	0.5	1.4×10^{-2}
Relaxed	1.8	3.1*	4.3*	0.6*	1	1.2	5.5×10^{-5}
Skin itchy	0.3	2.4*	3.2*	0.6	0.2	1	3.4×10^{-6}
Normal	4.8	1.5*	0*	2.7*	2.8*	1	7.6×10^{-8}
Drunken	0	0	0	0	0	NS	0.42
Nervous	0	0.2	0.9	1	0.2	NS	0.21
Nodding	0.1	0.4	1.2	0.5	0.3	NS	0.26

*Same as Table 1.

dose of naloxone did not increase scores on the Perception Scale significantly.

The Opiate Symptoms scale (Single Dose Questionnaire) scores for naloxone 150 mg and 300 mg demonstrated significant decreases over the placebo scores on the item, Normal (Table 4). The responses for naloxone on the Normal symptom scale were very consistent with seven of ten subjects scoring the naloxone doses lower than the placebo condition. The 150 mg dose of naloxone was scored as significantly less relaxing than placebo on the Relaxed symptom, while the 300 mg dose trended in the same direction. However, the Relaxed symptom scores were attributable to only three of ten men. Interestingly the scores for the symptom, Nervous, were not significantly different from placebo. The 300 mg dose of naloxone was scored significantly higher than placebo, morphine, and naloxone 150 mg on the symptom, yawning. This symptom was added to the Opiate Symptoms Scale in the "other" column.

Drug identification. The drug identification procedure demonstrated that subjects could identify the drugs included in the drug identification portion of the experiment. The chi square analysis of the five drug conditions versus the drug identifications demonstrated that there is a significant departure from a random arrangement. The p value is <0.001. The identification procedure and the results have been reported previously with reference to the ketocyclazocine and cyclazocine portion of the experiment [21]. In the drug identification procedure naloxone was identified as naloxone eight out of twenty times (40%). In contrast, placebo was identified as placebo 7 out of ten times (70%). Naloxone appeared to generate a vague discriminatory stimulus. It was identified as placebo five out of twenty times (25%) but was identified as ketocyclazocine twice (10%, cyclazocine twice (10%), and morphine thrice (15%). Placebo was identified more reliably than naloxone. Of the three incorrect placebo identifications, two identified placebo as naloxone (20%) and only one time was placebo identified as a drug with agonist properties (cyclazocine—10%).

The free form comments given by the subjects gave some insight into the kind of feelings induced by naloxone. The tabulation of descriptive words used by subjects to describe naloxone induced sensations and placebo induced sensations are presented in Table 5.

TABLE 5

DESCRIPTIVE COMMENTS FROM DRUG DISCRIMINATION PROCEDURES

Coments	Number of Times Listed by Subjects: Naloxone	Placebo
Blank/nothing/no effect	5	13
Tingling/pins and needles	1	1
Nausea/vomiting/stomach turning/sick	10	1
Headache	2	1
Up/mellow/easy going	2	2
Tired, sleepy/drowsy/lazy	10	2
Yawning/stretching	7	2
Spacey/buzz/speeded-up	6	0
Damp nose	2	0

Drug Similarity Rating Scale. The Drug Similarity Rating Scale results measure the relative differences in psychoactivity between the drug conditions as rated by the subjects (Fig. 2a). The results of this analysis with respect to ketocyclazocine and cyclazocine obtained in the same experiment have been reported previously [21]. Both doses of naloxone were judged by subjects as closer to placebo than to any other drug in the training set. The distance between the 150 mg dose of naloxone and placebo was 0.44. The distance between the 300 mg dose of naloxone and placebo was 0.34. The distance between the two doses of naloxone was 0.11 indicating a close similarity in the effects of the two doses. The diagrammatic representation of the data demonstrates that naloxone must be displaced off the direct line drawn between placebo and morphine in order to maintain the cor-

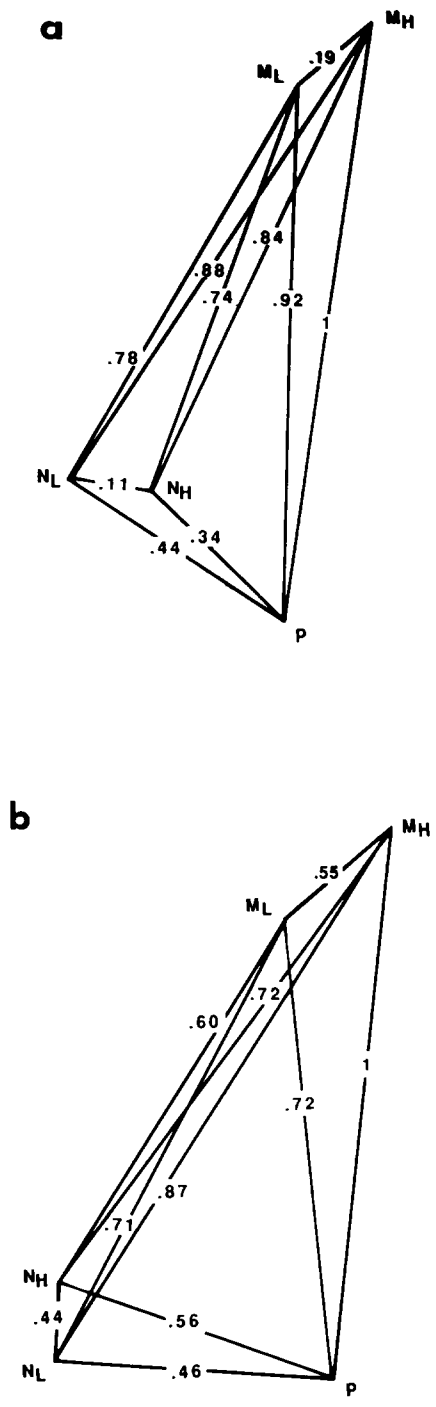

FIG. 2. (a) Drug similarity models represent relative differences as perceived by subjects between the 15 mg dose of morphine (M_L), the 30 mg dose of morphine (M_H), the 150 mg dose of naloxone (N_L), the 300 mg dose of naloxone (N_H) and placebo (P). The distances are expressed in three-dimensional space as a ratio with the distance from P to M_H. The distance is calculated as the square root of the quantity, the sum of the t-squares of the scores for a drug pair on each of the Drug Similarity questions, A to E. (b) ARCI Scalar models represent the scalar differences as calculated for the 23 drug-relevant subscales of the ARCI. The differences were calculated in relation to reference populations tested under a no drug condition for standardization [14].

rect distances from naloxone to morphine and placebo. Therefore a diagram of these distances in space requires, at minimum, a two dimensional representation. The representation of both doses of morphine and both doses of naloxone requires a three dimensional representation though the figure is generally a planar (two dimensional) shape.

ARCI. The results of the t-square analysis for the ARCI with respect to naloxone are seen in Fig. 2b. Like the DSR the distances between the naloxone doses and placebo are less than the distances between the naloxone doses and morphine. The 150 mg dose of naloxone is positioned 0.56 units from placebo and the 300 mg dose of naloxone is 0.46 units from placebo.

The pattern of spatial relationships among the drugs as measured on the ARCI resemble the relationships among the drugs as measured on the Drug Similarity Rating Scales. A comparison of the distances from the two models (DSR and ARCI) between drug condition pairs was performed using a Deming orthogonal regression [7]. This procedure resulted in a correlation coefficient between the ARCI score distances and the drug similarity ratings of perceptual distances of 0.85. However, one striking difference was noted. The relative distance of morphine 15 mg to morphine 30 mg was very much greater as measured by the ARCI technique as compared to the DSR (0.19 vs. 0.55).

Experiment II

Seven subjects had plasma samples collected for prolactin assay after naloxone 210 mg and placebo was given. The results demonstrate that prolactin concentrations in the plasma were increased until 120 minutes after the naloxone dose as compared to placebo. After 120 minutes the prolactin concentrations fell below those obtained after placebo though this decrease was significant only at the 240 min time point (Fig. 3). The two-way analysis of variance of the naloxone and placebo conditions demonstrated that there was a significant difference of prolactin concentration as a function of time ($p<4.3\times10^{-6}$) and a significant interaction of the drug condition and time ($p<1.5\times10^{-3}$). However, mean prolactin concentrations did not differ significantly between the naloxone and placebo conditions. The interaction of drug condition and time for the prolactin concentration underscores the fact that the pattern of response of prolactin under the experimental conditions was altered with respect to time by naloxone.

DISCUSSION

The volunteer subjects participating in our study had histories of opioid abuse. All were carefully screened for the presence of physical dependence. Although none had any evidence of physical dependence, it is possible that previous opioid use could result in drug responses that differ from those of a drug-naive group. However, our results are in general agreement with the reports of other investigators studying other subject populations [3, 4, 12, 19, 34, 37]. Therefore, it is possible that our experimental results reflect the basic pharmacologic activity of very large doses of naloxone in man.

Naloxone, at doses of 150 mg and 300 mg, had pharmacologic activity in man. The results of the "Feel Drug" scale, the drug identification procedure and the Opiate Signs scores indicate that naloxone is psychoactive. Furthermore, the pattern of activity measured by the "Feel Drug" scale has the appearance of a drug time-action curve, i.e., an as-

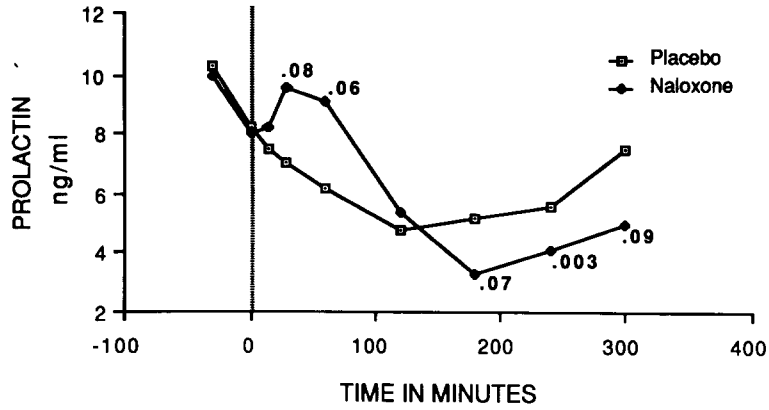

FIG. 3. Plasma prolactin concentrations for 7 subjects (Experiment II) plotted versus time. Overall the plasma concentrations of prolactin did not differ between the two conditions. However, there was a significant ($p<0.05$) interaction between the drug conditions and time. The numbers on the graph are the p values for t-tests comparing placebo and naloxone 210 mg at particular time points.

cending and descending portion. But the subjective sensation of naloxone is subtle. The effects are not easily quantified with the measures we used. Neither those scales which are useful for measuring morphine-like effects nor those useful for measuring morphine withdrawal were sensitive to the effects of naloxone. Yet, in the free form descriptive comments subjects used the words, "yawning, sleepy, tingling, buzz and nausea" to describe their feelings (Table 5).

Our study is in general agreement with previous reports of subjective mood states after naloxone. Jasinski *et al.* [18] reported a statistically significant score on the Opiate Signs scale after 24 mg of naloxone given intramuscularly. Their item analysis revealed a high incidence of "sleepy" items in the observers questionnaire. Grevert *et al.* [12] reported increases in the POMS scores for confusion-bewilderment and fatigue-inertia during naloxone intravenous infusions of 6 mg/hr in twelve normal male subjects. On the basis of the POMS scores they concluded that naloxone caused a slightly aversive mood state. In a study of nine healthy volunteers given 0.3–4 mg/kg of naloxone intravenously, Cohen *et al.* [3] reported subjective feelings of "rush" or "buzz," tingling, numbness, dizziness, reluctance to move, sweating, yawning, and nausea. POMS scores were elevated on the confusion-bewilderment, tension-anxiety, anger-hostility, and depression-dejection subscales in their sample. However, they did not find increases on the fatique-inertia subscale as observed by Grevert *et al.* [12]. Jones and Herning [19] studied eighteen people without a history of drug abuse. They found a constellation of symptoms distinguished between intravenous placebo and naloxone injections of 3–20 mg. The symptoms that were useful distinguishing features of naloxone included loss of appetite, tears, yawning, restlessness, and sweating. Feelings of cold and muscle discomfort correlated negatively with naloxone administration. They also reported that the Profile of Mood States (POMS) scores were increased on the item, confusion.

The question arises as to whether these observations are the results of antagonist effects or agonist effects of naloxone at opioid receptors. Although signs such as yawning and sweating are associated with morphine abstinence syndrome, symptoms such as rush, dizziness, buzz, tingling and sleepiness can describe morphine agonism. Still other symptoms like confusion, restlessness, and anxiety can describe morphine abstinence but are also very appropriate descriptions of the effects of ketocyclazocine, an opioid with kappa activity [21]. Three of the subjects in Jones and Herning's study experienced intense effects after naloxone: one, acute depression; the second, visual illusions; the third, extreme irritability [19]. These descriptions in particular are very similar to the effects of ketocyclazocine and cyclazocine in man [21].

Naloxone in doses up to 20 mg may not alter plasma prolactin concentrations in normal volunteers [27,35]. At doses up to 15 mg, Rubin *et al.* [30] reported a slight decrease in the plasma prolactin levels in man between 60 and 240 minutes after the drug was given. Concentrations of prolactin are known to increase after acute morphine administration to animals and man [2, 8, 33]. Under conditions of opiate withdrawal, serum prolactin is unchanged in rats under nonstressed conditions [26]. In our study the pattern of plasma prolactin concentrations was altered by naloxone. Prolactin concentrations peaked between 30 and 60 minutes following naloxone adminstration. After 120 minutes the prolactin concentration following naloxone fell below the concentrations observed after placebo. This pattern is reminiscent of a homeostatic biphasic response after stimulation. Since no peaks were observed in the placebo prolactin response we assume that our experiment is similar to the nonstressed condition in the animal experiments of Mioduszewski *et al.* [26]. Therefore, we conclude that the prolactin response to large doses of naloxone in man is compatible with opiate agonism and not withdrawal and differs from doses of naloxone between 8 and 20 mg. However, the magnitude of the prolactin response (Fig. 3) was very small compared to the 29 ng/ml mean prolactin increase reported by Tollis [33] after 10 mg doses of morphine (Table 6).

Among the physiologic measures naloxone caused an increase in the standing blood pressure, a decrease in body temperature and a strong trend toward a decrease in the respiratory rate but no changes in pupil size. Other investigators studying human volunteers have found similar physiologic responses after naloxone administration although there are some conflicting reports. Cohen *et al.* [4] reported a significant increase of systolic blood pressure but

TABLE 6

PROPERTIES OF LARGE DOSES OF NALOXONE AS COMPARED TO MORPHINE AGONISM AND WITHDRAWAL STATES

Measure	Agonism	With-drawal	Naloxone 150–300 mg
Miosis	−	+	0
Blood Pressure	+	+	+
Respirations	−	+	−(tr)
Temperature	−	+	−
Prolactin Plasma Levels	+	0	+

no increase in the respiratory rate after 0.3–4 mg/kg doses of naloxone given to volunteers. Willer *et al.* [36] reported that 1.2 mg of naloxone did not change tidal volume, inspiratory or expiratory durations, respiratory rate nor the partial pressure of carbon dioxide in blood [$PaCo_2$]. Volavka *et al.* [34] reported decreased temperature after 10–20 mg injections of naloxone and Zilm [37] reported decreased core temperature after 1.2 mg of naloxone. In comparison, temperature and respiration increase in opiate withdrawal syndromes, whereas, blood pressure increases both during agonism and withdrawal. Pupil size decreases with opiate agonism and increases during withdrawal.

Some authors have suggested that the activity of naloxone is not agonist-antagonist but a withdrawal from endogenous opioids [3, 4, 12]. A comparison of the physiologic activity profile of the large doses of naloxone used in our experiment with the profile of the activity of opioid mu agonists and the pattern of responses observed in withdrawal from morphine shows little similarity between large doses of naloxone and opiate withdrawal. There is more similarity between naloxone and opioid agonism (Table 6).

With regard to the nature of naloxone psychoactivity, the DSR and ARCI models are of interest. Naloxone has a vector in the direction of morphine. That is, the naloxone-morphine distances are shorter than the morphine-placebo distances suggesting some similarity to morphine. However, the position of naloxone indicates that an even larger vector exists at right angles to the morphine-placebo axis. This component cannot be interpreted as there was no standard drug or withdrawal conditions included in the study that shared a prominent vector in the same direction.

The DSR and ARCI models for the set of drugs in the study are similar in shape. This similarity has been noted with respect to ketocyclazocine, cyclazocine, morphine, placebo models previously reported [21]. The striking difference between the morphine 30 mg and morphine 15 mg distances in the two models appears to be caused by a lack of sensitivity of the ARCI to the low morphine dose in this population. The DSR is a direct method of determining and quantifying psychoactive differences in which subjects estimate a difference between drug pairs whereas the ARCI is an indirect method because subjects answer questions related to mood and feeling states without considering the drug experience per se. The fact that the models derived from the two techniques appear to be convergent lends internal validity to this method of mapping psychoactivity of drugs and supports the finding of the presence of 2 vectors prominent in the psychoactivity of naloxone; one morphine-like, another larger one, an unknown dimension.

A substitution of an allyl group on the nitrogen atom of morphine and levorphanol in the synthesis of nalorphine and levallorphan confers an activity pattern distinct from morphine-like agonists. This activity has been termed agonist-antagonist. Initially, naloxone, the allyl substituted product of oxymorphone, was found to have little or no agonist activity when compared to nalorphine and levallorphan. On the basis of our observations of subjective, objective, physiological and hormonal responses, naloxone does not have a clear antagonistic or agonistic subjective effect profile in man in the dose range of this study. Naloxone has similar effects to nalorphine and levallorphan but the intrinsic activity and potency are less [18]. Our results are most compatible with a mixed agonist-antagonist profile of activity.

Our experiment was designed to determine the pharmacologic similarity between opioid mu agonists and very large doses of naloxone on some measurements of interest. We conclude that there is some similarity in the responses after mu agonists and the response after very large doses of naloxone. However, this similarity may be unrelated to opioid receptor specific interactions. It is possible that the effects we have observed are the result of naloxone interacting with nervous system efferents of opioid sensitive neurons or even other neuronal units completely unrelated to opiod activity.

Nevertheless, we believe our observations may have importance in the interpretation of experiments in which doses of naloxone much greater than that necessary for mu antagonism are employed. Under such circumstances large doses may possess agonist action at opioid receptors.

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