0022-3565/99/2892-0936$03.00/0
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Vol. 289, No. 2
Printed in U.S.A.

JPET 289:936–945, 1999

Relative Potency of *levo*-α-Acetylmethadol and Methadone in Humans under Acute Dosing Conditions[1]

THOMAS EISSENBERG,[2] MAXINE L. STITZER, GEORGE E. BIGELOW, AUGUST R. BUCHHALTER,[2] and SHARON L. WALSH

Behavioral Pharmacology Research Unit, Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, Maryland

Accepted for publication December 29, 1998 This paper is available online at http://www.jpet.org

ABSTRACT

levo-α-Acetylmethadol (LAAM) and methadone are full μ-opioid agonists used to treat opioid dependence. Current labeling indicates that LAAM is less potent than methadone. Clinical studies have not determined the relative potency of these drugs. This study compared the effects of acute doses of LAAM and methadone and also examined the ability of naloxone to reverse their effects. Five occasional opioid users received once weekly doses of either placebo, LAAM, or methadone (15, 30, or 60 mg/70 kg p.o.) in agonist exposure sessions and then received naloxone (1.0 mg/70 kg i.m.) 24, 72, and 144 h after agonist exposure. Subject-rated, observer-rated, and physiological measures were assessed regularly. Comparisons of physiological and subjective measures collected in agonist exposure sessions indicate that LAAM is not less potent than methadone under acute dosing conditions. For some measures, LAAM was significantly more potent. Three subjects who entered the study were withdrawn for safety reasons due to greater than anticipated and clinically relevant respiratory depression after receiving 60 mg of LAAM. Naloxone did not fully reverse the pupil constriction produced by 60 mg of LAAM. Acute agonist effects suggest that LAAM may be more potent than methadone and more potent than current labeling indicates. An accurate LAAM:methadone relative potency estimate will aid determination of adequate doses for opioid-dependent patients inducted onto LAAM and for methadone maintenance patients who choose to switch to more convenient thrice-weekly LAAM.

levo-α-Acetylmethadol (LAAM) is a long-acting, full μ-opioid agonist (Fraser and Isbell, 1952) with demonstrated efficacy as an opioid dependence pharmacotherapy (Ling et al., 1976, 1978). Both LAAM and methadone, another full μ-opioid agonist, are approved by the U.S. Food and Drug Administration as opioid dependence treatment medications, primarily because they blunt the effects of concurrently administered illicit opioids and suppress opioid withdrawal (Dole and Nyswander, 1965; Jaffe et al., 1970; Jaffe and Senay, 1971; Zaks et al., 1972; Kreek, 1992). One advantage of LAAM over daily methadone treatment is that LAAM's long duration of action, attributed primarily to its two active metabolites nor-LAAM and dinor-LAAM (McMahon et al., 1965; Billings et al., 1973, 1974; Henderson et al., 1977), allows for thrice-weekly dosing.

Treatment guidelines and product labeling suggest that LAAM is less potent than methadone. For example, labeling indicates that methadone-maintained patients should receive an initial dose of LAAM that is 1.2 to 1.3 times their daily methadone dose (i.e., a 0.8:1.0 methadone:LAAM relative potency ratio; Medical Economics Data, 1998). This recommendation implies that a higher LAAM dose, relative to a given methadone dose, is necessary to achieve the same therapeutic effect. Review of the scientific literature fails to reveal any empirically derived clinical data regarding the relative potency of methadone and LAAM, because no study has been designed a priori to determine this information. Instead, current product labeling may be based on preclinical data that separated the effects of LAAM from those of its active metabolites (e.g., Vaupel and Jasinski, 1997) or outcome data from clinical trials that were not designed to estimate relative potency optimally (e.g., Jaffe et al., 1970; Ling et al., 1976).

Recent comparisons of the acute effects of LAAM and methadone across clinical laboratory studies suggest that the

Received for publication July 23, 1998.
[1] This research was supported by U.S. Public Health Service Grants K05-DA00050, P50-DA05273, R01-DA04011, R29-DA11082, and T32-DA07209.
[2] Present address: Department of Psychology, Virginia Commonwealth University, Richmond, VA 23298-0205.

ABBREVIATIONS: LAAM, *levo*-α-acetylmethadol; ARCI, Addiction Research Center Inventory; SCID, Structured Clinical Interview for the DSM-IV; VAS, Visual Analog Scales; WOW 194, the most significant Weak Opiate Withdrawal items (scale 194) of the ARCI; MBG, morphine-benzedrine group ("euphoria" scale); PCAG, pentobarbitol-chlorpromazine-alcohol group ("sedation" scale); LSD, lysergic acid diethylamide ("dysphoria" scale).

potency of LAAM may be underestimated. For example, pupil constriction 12 h after acute administration of 40 mg of LAAM appears approximately equal to that observed 3 h after 60 mg of methadone (Walsh et al., 1994, 1998). Unfortunately, neither past clinical trials nor cross-study comparisons allow within-subject analysis of the response to multiple dose levels of each medication, as is customary for relative potency estimation (Finney, 1978). Thus, no clinical study to date has been designed to produce the data on which an accurate estimate of the LAAM:methadone relative potency ratio can be based. The current study was designed to test the relative potency of acute doses of LAAM and methadone in humans and to incorporate the activity of the metabolites of LAAM.

Administration of the opioid antagonist naloxone after acute opioid agonist pretreatment can reverse agonist effects and may precipitate opioid withdrawal (e.g., Bickel et al., 1988; Wright et al., 1991). Reversal of acute agonist effects is influenced by naloxone dose but may also be influenced by agonist potency and/or half-life (Ellenhorn et al., 1997). Similarly, the likelihood of precipitating opioid withdrawal after acute agonist administration, revealing physical dependence (e.g., Nutt and Jasinski, 1974; Higgins et al., 1992), is related to several factors including agonist half-life (Greenwald et al., 1996). For methadone, physical dependence can be detected up to 96 h after a single, 30-mg dose (Stitzer et al., 1991), and larger doses (e.g., 40 mg) may produce even longer-lived acute physical dependence (Nutt and Jasinski, 1974). Physical dependence after an acute LAAM dose has been demonstrated in preclinical studies (e.g., Vaupel and Jasinski, 1997), but its occurrence and duration have not been studied in humans. Determining the ability of an antagonist to reverse agonist effects fully is critical, because antagonist treatment is the standard of care for opioid overdose (Ellenhorn et al., 1997). LAAM's potency, long half-life, and active metabolites may influence an antagonist's ability to reverse LAAM's effects as well as the duration and intensity of LAAM's acute physical dependence.

This study assessed the relative potency of acute doses of LAAM and methadone using a variety of measures. Opioid users, without physical dependence, received once weekly doses of placebo, LAAM, or methadone, and the character and intensity of the resulting agonist effects were assessed over the subsequent 24 h. In the absence of any previous relative potency data and based on recent cross-study comparisons (Walsh et al., 1994, 1998), equal doses were tested (i.e., 15, 30, and 60 mg/70 kg of LAAM and methadone). The study also assessed naloxone's reversal of LAAM and methadone's acute effects and the physical dependence engendered by single doses of these agonists. Volunteers received naloxone at three intervals over a 1-week period after acute agonist exposure and were assessed for signs and symptoms of precipitated withdrawal.

Materials and Methods

Subjects

Subjects were recruited by word of mouth, newspaper advertisements, and circulation of flyers. Nine occasional opioid users (eight male; all African-American) gave their informed consent to participate. Opioid use history was verified by self-report and the presence of at least one opioid-positive urine specimen before inpatient admission. Absence of physical dependence was verified by requiring an opioid-free urine specimen (and the absence of overt withdrawal signs) on the day of admission. Four subjects failed to complete the protocol (see Table 1 and *Results*). Data reported here are from the five participants (all black males) who completed the entire 7-week protocol.

Subjects were ages 27 to 43 (mean, 35 years) and reported using heroin 9 to 15 days of the 30 days before admission (mean, 12.2). They reported using heroin for 6 to 26 years (mean, 12.0). Despite the absence of physical dependence in all subjects (i.e., absence of watery eyes, gooseflesh, runny nose, etc., at admission), four of the five subjects who completed the protocol received current psychiatric diagnoses of opioid dependence based on the E module of the Structured Clinical Interview for the DSM-IV (SCID; First et al., 1994), administered after admission. Two of the five subjects had a history of prior treatment for their opioid dependence (one reported five treatment episodes; the other reported three treatment episodes). These previous treatment episodes consisted of nonmethadone or methadone-assisted detoxification. No subjects reported previous maintenance treatment with methadone or LAAM.

All subjects reported that they were cocaine users, using cocaine 4 to 16 days of the 30 days before admission (mean, 10.6). They reported using cocaine for less than 1 to 15 years (mean, 5.8). All subjects received current psychiatric diagnoses of cocaine dependence by SCID interview. SCID results also indicated that three of the five subjects were currently alcohol dependent, one used sedatives, three used cannabis, and none used stimulants other than cocaine. Four subjects smoked cigarettes, with reported intake ranging from 7 to 19 cigarettes/day (mean, 11.5 cigarettes/day).

Before enrollment, each subject received medical evaluation, including physical examination, electrocardiogram, hematology, and

TABLE 1
Order in which each agonist dose was administered to each subject

Subject	Relative Potency Assessment Session no.							Reason for Discharge
	1	2	3	4	5	6	7	
Completers								
03	60M	15 L	30M	30 L	15M	60 L	P	Completed protocol
04	15 L	30 L	60M	60 L	30M	P	15M	Threatening research staff
05	30M	60M	15M	15 L	P	30 L	60 L	Completed protocol
06	60 L	P	30 L	15M	15 L	30M	60M	Completed protocol
07	15M	30M	P	60M	60 L	15 L	30 L	Completed protocol
Noncompleters								
01	60M	15 L	30M	30 L	15M	60 L		Clinically significant respiratory depression
02	15 L							Illness unrelated to study medication
08	30 L	60 L						Clinically significant respiratory depression
09	30 L	60 L						Clinically significant respiratory depression and disorientation

Doses are in mg/70 kg p.o.; L, LAAM; M, methadone; P, placebo. Doses were ordered by a single, seven-condition Williams square (Jones and Kenward, 1989). Shaded area indicates last agonist dose received before discharge. Each agonist dose was administered once, and agonist administrations were separated by 7 days.

urinalysis testing. Pregnant women and individuals with significant psychiatric disorders or medical conditions (other than substance abuse or dependence) were excluded from study participation.

Informed Consent

This study was approved by the local Institutional Review Board, and all subjects provided written informed consent before participation. Subjects were informed that they were eligible to participate based on their occasional opioid use, that they would receive opioid agonists and/or antagonists, and that they might experience opioid euphoria and/or withdrawal as part of their participation.

Setting

Subjects resided on a closed 14-bed behavioral pharmacology research unit (Walsh et al., 1995) for ~7.5 weeks. On nonsession days, subjects' access to food, drink, and cigarettes was unrestricted. On session days, subjects were allowed to eat breakfast before 8:00 AM, lunch between 1:00 and 2:00 PM, and an evening meal between 6:00 and 7:30 PM. Smoking was not permitted until after session. Subjects were on a caffeine-free diet throughout their inpatient participation.

Beginning several days after inpatient admission, subjects' urines were tested periodically to verify the absence of nonprotocol-related opioids, cocaine, or benzodiazepines using the enzyme-multiplied immunoassay technique (Syva Corp., Palo Alto, CA). All urine drug tests during the residential stay were negative for nonprotocol-related drugs.

Drugs and Drug Administration

LAAM hydrochloride oral solution (10 mg/ml; Roxane Laboratories, Columbus, OH) and methadone hydrochloride (10 mg/ml; Mallinckrodt, St. Louis, MO) were prepared in 40-ml doses using different tasting, different colored, sugar-free, alcohol-free, sweetened vehicles (LAAM; Ora-Sweet SF, Paddock Laboratories, Inc., Minneapolis, MN; methadone/cherry concentrate, Mallinckrodt, St. Louis, MO) and water (1:4) with 12 ng/ml denatonium benzoate (Bitrex, Macfarlan Smith, Ltd., Mt. Vernon, NY) as an additional flavor mask. Placebo methadone and LAAM were matching vehicle (40 ml) without active drug. Oral medication administration was supervised by staff to ensure compliance.

Naloxone hydrochloride (10 mg/ml; Du Pont Merck Pharmaceutical Co., Wilmington, DE) challenge doses (1 mg/70 kg i.m.) were prepared by extracting the appropriate volume of commercial drug solution for each dose and diluting it up to a volume of 2 ml with 0.9% bacteriostatic saline for injection. All placebo injections were 2 ml of saline. Injections were given in the deltoid muscle of the left or right arm (alternated across sessions).

All medications were administered at 9:30 AM, using double-blind and triple-dummy procedures. Thus, research assistant, administering nurse, and subject were unaware of drug doses. Subjects received an i.m. injection and two differently flavored p.o. administrations on each session day; one or none of these was active.

Experimental Conditions

There were seven experimental conditions: placebo; LAAM (15, 30, and 60 mg/70 kg p.o.); and methadone (15, 30, or 60 mg/70 kg p.o.) administered as single acute doses once weekly. Each experimental condition included a single 7.5-h relative potency assessment session and three 3.5-h acute physical dependence assessment sessions. In each relative potency session, placebo or one of the six active agonist doses was administered. In each acute physical dependence assessment session, which occurred 24, 72, and 144 h after agonist exposure, 1.0 mg/70 kg i.m. naloxone was administered.

All sessions were run in a quiet testing room separate from the residential unit (Schuh et al., 1996). The testing room was equipped with a Macintosh SE microcomputer (Apple Computer, Cupertino, CA) used to record all subject- and observer-rated measures and all physiologic measures except for pupil diameter and respiration. A research assistant, present throughout each session, escorted subjects to the testing room at approximately 8:50 AM. Sessions began at 9:00 AM, after ~10 min of acclimation to the testing room. Agonist exposure sessions ended at ~4:45 PM, although data collection continued on the residential research unit to 9:30 PM. (i.e., 12 h after drug administration). A 12-h data collection period was chosen to encompass the time necessary to achieve peak effects after oral LAAM administration (Walsh et al., 1998). Antagonist challenge sessions ended at 12:30 PM, and data collection continued on the residential research unit through 2:30 PM. (i.e., 5 h after drug administration).

Subject-Rated Measures

Data from an array of subject-rated measures were collected 30 min before and at regular intervals after drug administration within each experimental session. Postsession measures were assessed hourly. Self-report measures consisted of visual analog scales (VAS), adjective rating scales, the short form of the Addiction Research Center Inventory (ARCI; Martin et al., 1971), and scale 194 of the ARCI, labeled in the manual of ARCI scales as the "most significant weak opiate withdrawal items" of the ARCI (Haertzen, 1974) and referred to here as the WOW 194. Responses to the VAS items were assessed 5, 10, and 15 min after drug administration and at 15-min intervals thereafter until the end of each session. All other measures were assessed at half-hour intervals during each session.

VAS. VAS items were presented on the computer monitor as a 100-mm horizontal line, anchored on the left with "not at all" and on the right with "extremely." Subjects were instructed to move the cursor (a vertical line) along the horizontal line with the mouse and to click the mouse button when they had reached the position on the line most closely reporting their response to the following items: "How HIGH are you?", "Do you feel any DRUG EFFECT?", "Does the drug have any GOOD EFFECTS?", "Does the drug have any BAD EFFECTS?", "Do you LIKE the drug?", "Do you DISLIKE the drug?", and "How much do you desire OPIATES right now?"

Adjective Rating Scales. The three adjective rating scales (withdrawal adjective scale, agonist adjective scale, and Fraser scale), identical with those reported elsewhere (e.g., Walsh et al., 1994), were presented as 5-point items, where 0 = not at all, 1 = a little bit, 2 = moderately, 3 = quite a bit, and 4 = extremely. The 21-item withdrawal adjective scale consisted of the sum of equally weighted items indicative of opioid withdrawal, such as yawning, watery eyes, runny nose, muscle cramps, etc. The 16-item agonist adjective scale consisted of the sum of equally weighted items indicative of opioid agonist effects, such as: turning of stomach, nodding, skin itchy, heavy or sluggish feeling, etc. The Fraser scale consisted of 10 weighted items indicative of opioid agonist effects. Items (and their weights) were: turning of stomach (1), skin itchy (2), relaxed (1), coasting (2), talkative or soapboxing (1), pleasant sick (1), drive (2), sleepy (2), drunken (1), and nervous (1). All items were intermixed to form a single checklist. Ratings of the individual items on each scale were summed to form the scale scores.

ARCI. The short form of the ARCI consisted of 49 true-false items. These 49 items comprised five empirically derived subscales: the amphetamine and benzedrine group subscales (both sensitive to amphetamine-like effects), MBG (sensitive to euphoric effects), the PCAG (sensitive to sedative effects), and the LSD subscale (sensitive to somatic and dysphoric changes).

WOW 194. The WOW 194 consisted of 21 true-false items from the ARCI and is described in detail elsewhere (Haertzen, 1974). The WOW 194 consists of 16 items to which a "true" response is indicative of withdrawal and 5 items to which a "false" response is indicative of withdrawal; these items are intermixed to form a single scale. The score is the number of withdrawal indicative responses.

Observer-Rated Measures

Data from two observer-rated measures were collected 30 min before drug administration and at 15-min intervals thereafter until the end of each session. The observer-rated measures consisted of a modified version of Himmelsbach's (1941) withdrawal severity scale and an observer's adjective rating scale.

Modified Himmelsbach. To assess signs of precipitated withdrawal objectively, observations of each subject in each condition were made by a trained research assistant, blind to dose, who was present throughout the session. The observer rating consisted of a modified Himmelsbach (1941) withdrawal severity scale, demonstrated previously to be sensitive to opioid withdrawal (Eissenberg et al., 1996). On this measure, each of seven signs was rated by an observer on a 3-point scale where 0 = none, and 1 and 2 were graded ratings individualized for each sign. The signs were: yawning, lacrimation, rhinorrhea, perspiration, gooseflesh, bowel sounds, and restlessness, and individual item scores were summed to form the scale score.

Observer Adjective Rating Scale. To assess further the effects of agonist and antagonist administration in each session, the research assistant rated each subject on a 5-point scale from 0 (not at all) to 4 (extremely) in response to 12 adjectives or phrases as reported elsewhere (e.g., Walsh et al., 1995). The 12 adjectives or phrases were: nodding, scratchy, magnitude of drug effect, restlessness, talkative, sleepy/sedated, energetic, irritable, friendly, vomiting, drunken, and nervous.

Physiological Measures

Five physiological measures were monitored continuously in the testing room: percentage of oxygen saturation, pulse rate, skin temperature, systolic blood pressure, and diastolic blood pressure (Noninvasive Patient Monitor model 506, Criticare Systems, Waukesha, WI). The percentage of oxygen saturation, pulse, and skin temperature were measured automatically once per minute. Blood pressure was recorded once every 3 min. Continuously monitored physiological data were averaged into 15-min bins for ease of analysis. Additionally, respiration rate was assessed manually at 15-min intervals by counting the number of respirations that occurred in 15 s. Data were multiplied by 4 to attain a measure of respirations/min. Pupil diameter was determined from photographs taken in ambient room lighting using a Polaroid (Cambridge, MA) camera fitted with 2X magnification.

Missing Data

Computer malfunction, subject discomfort (e.g., temporary discomfort from the blood pressure cuff, bathroom breaks), or human error resulted in 0.6% missing data. In most cases, one, two, or three consecutive data points were missing from within a session, and these missing values were replaced by the average of the single values surrounding the missing points. However, in one case, computer error led to a failure to store the physiological data during a subject's (03) 60 mg of LAAM relative potency assessment session. All subject-rated, observer-rated, and pupil diameter data were stored. In this case, physiological data from the four subjects for whom complete data were collected were analyzed. Also, one subject (04) was discharged for threatening research staff before completing the 72- and 144-h naloxone challenge sessions within the 15 mg of methadone agonist condition. Because of this reduction in sample size and the fact that carryover effects from some agonist doses may have influenced precipitated withdrawal effects, data from the 72- and 144-h naloxone challenge sessions are not discussed or presented.

Data Analysis

Measures Analyzed. The measures analyzed included seven VAS scales, summed scores from the Agonist, Withdrawal, and Fraser adjective scales, five derived subscales from the ARCI, the summed score from the WOW 194, the summed score from the modified Himmelsbach and observer adjective measures, and all physiological measures except for respiration rate and percentage of oxygen saturation. Respiration rate and percentage of oxygen saturation were not analyzed because these variables were influenced systematically when research staff intervened to maintain subject safety. That is, subjects were routinely instructed to take a few deep breaths whenever the percentage of oxygen saturation dropped below 95%; this intervention, necessary for completion of the study, tended to obscure the effects of higher doses of LAAM and methadone on these measures where substantial respiratory depression and sedation were often observed. For all repeated measures analyses, significance levels were adjusted for violations of the sphericity assumption using Huynh-Feldt corrections. Where appropriate, a measure of effect size (η^2) is provided.

Relative Potency Assessment

Time Course of Drug Effects. Data from the seven agonist exposure sessions were entered into a two-factor repeated measures ANOVA, with drug condition (placebo, 15, 30, and 60 mg/70 kg of LAAM, and 15, 30, and 60 mg/70 kg of methadone) and time as the factors. The number of levels for the time factor differed across measures. For VAS and pupil measures, the time factor consisted of 36 levels (−30, 5, 10, 15, 30, 45, . . . 405, 420, 480, 540, 600, 660, and 720 min postdrug administration). For non-VAS subjective measures, the time factor had 20 levels (−30, 30, 60, 90, . . . 390, 420, 480, 540, 600, 660, 720 min postdrug administration). For observer-rated measures, the time factor consisted of 29 levels (−30, 15, 30, 45, . . . 405, 420 min postdrug administration), and for physiological measures, the time factor consisted of 36 levels (−30, −15, 0, 15, . . . 660, 720). The mean square error terms for the condition × time interaction were used to conduct Tukey's honestly significant difference test, which was used for comparing placebo with each of the drug conditions at each time point. Comparisons for which $P \leq .05$ are reported as significant.

Comparison of Methadone and LAAM Agonist Effects. To compare the agonist effects of each medication, peak effects within each agonist exposure session were determined for each subject and each variable using the data from all postdrug time points. Raw data were used for all variables. Peak effects rather than areas under the curve were determined for agonist exposure data because between-drug areas under the curve measures (i.e., methadone and LAAM) would be confounded by differing durations of action. Peak effects for each variable were analyzed using a one-factor repeated measures ANOVA and Tukey's honestly significant difference test ($P \leq .05$ reported as significant) was used to evaluate treatment condition mean differences.

To compare the agonist effects further, peak effect data from measures where significant main effects of dose were observed were analyzed further using the Finney (1978) method for parallel line bioassays. The analysis of parallel line bioassays is used to determine the relative potency of two compounds. This analysis was used to determine that the dose-response functions (excluding placebo) of LAAM and methadone did not differ with respect to linearity and parallelism ($P > .05$) and showed slopes significantly different from 0 ($P < .01$) without differences in effect magnitude across drugs ($P > .05$). Six-point bioassays were used for all measures (three doses per drug). Data from all measures meeting these criteria were used to calculate relative potency estimates and 95% confidence intervals for those estimates.

Assessment of the Effects of Naloxone

All five subjects completed all 24-h postagonist naloxone challenge sessions, but only four subjects completed all 72- and 144-h sessions. Carryover effects from some agonist doses were apparent on many subjective measures at the baseline assessment timepoint of the 24-h postagonist session. For these reasons, discussion of the effects of

naloxone challenge are limited to naloxone-induced reversal of pupillary constriction at 24 h. Time course data from the 24-h postagonist session, which all subjects completed, were analyzed in a two-factor (agonist dose condition, session time) ANOVA. The mean square error terms for the condition × time interaction were used to conduct Tukey's honestly significant difference test as above.

Results

Subject Disposition

Of the nine subjects who consented to participate in this protocol, five received all agonist doses as scheduled. Table 1 shows doses received, order of dose presentation, and reason for subject discharge for all subjects. Of the four subjects who failed to receive all agonist doses, one (02) was discharged after the first agonist dose due to illness unrelated to the study medication. The three other noncompleters were discharged from the study due to clinically significant respiratory depression (i.e., <6 breaths/min and/or percent blood oxygen saturation <90) that occurred after 60 mg/70 kg of LAAM administration. Importantly, one subject (01) tolerated 60 mg of methadone without incident but nonetheless experienced clinically significant respiratory depression after 60 mg of LAAM administration. For all subjects, constant medical monitoring assured their safety, although these effects may have been life-threatening in a less controlled environment. As a medical intervention, each subject received i.m. naloxone followed by p.o. naltrexone; all signs of opioid toxicity quickly resolved. The study was terminated after the third such event to avoid further risk to research participants, despite the fact that the initial goal was for seven subjects to complete the protocol. Inspection of previous heroin use, treatment history, and other demographic variables revealed no clear subject-specific explanation of why the 60 mg of LAAM dose produced these unexpected effects in three subjects.

Relative Potency Assessment

Time Course of Agonist Effects. Both LAAM and methadone produced orderly dose- and time-related effects on multiple variables reflective of opioid agonist effects. Highly significant condition by time interactions [i.e., $F(210,480) > 2.7$; Ps $< .009$] were observed for VAS ratings of "high", "any drug effect," "good drug effect," and "like the drug," for the Fraser adjective scale, observer ratings of nodding and magnitude of drug effect, and pupil diameter. Figure 1 shows the time course of LAAM and methadone effects for two representative indices of agonist effects: the "Do you LIKE the drug?" VAS and pupil diameter. Both agonists produced significant dose-related effects on these measures. The average latency to peak effect was shorter for methadone (2–4 h) than for LAAM (typically 4–8 h), depending on the measure. The effects of LAAM were generally longer lived than those of methadone, with statistically significant subjective effects of 30 and 60 mg of LAAM persisting for up to 12 h compared with 6 to 10 h for methadone. Most importantly, the magnitude of agonist effects produced by each dose of LAAM was generally equal to or (nonsignificantly) greater than for equal doses of methadone. This observation was consistent across most measures traditionally associated with opioid action (e.g., VAS ratings of high and good drug effects; observer ratings of nodding and scratchy, and others).

Peak Agonist Effects. Table 2 summarizes the peak effect analyses for all subject-rated, observer-rated, and physiological outcome measures sensitive to agonist effects. Measures chosen for sensitivity to withdrawal (e.g., bad effects and dislike the drug VAS, antagonist adjective scale, and modified Himmelsbach) are not displayed. Significant condition (placebo, LAAM, or methadone) effects were obtained on several visual analog scales, the agonist and Fraser adjective scales, one of the five ARCI subscales, 3 of 12 observer-rated items, and one of five physiological measures (pupil diameter). For both LAAM and methadone, peak agonist effects were dose related on nearly every measure where significant effects were observed. On many measures, the 60 mg of LAAM dose produced effects that were significantly greater than the 15 mg LAAM dose; a significant difference between 15 and 60 mg of methadone was observed for one measure, the agonist adjective scale. Of the measures in Table 2 that attained statistical significance, observed effect sizes (η^2) ranged from 0.42 to 0.73, yielding substantial statistical power [i.e., $(1 - \beta) > 0.78$].

Table 2 displays the relative potency estimates and corresponding 95% confidence intervals for each measure that met the criteria for a valid bioassay. The relative potency estimates in Table 2 are expressed as the mg of methadone required to produce the same effect as 1 mg of LAAM. In all cases, the relative potency estimates exceed 1.0 (geometric mean, 1.45), suggesting that >1.0 mg of methadone is required to achieve the magnitude of effect produced by 1.0 mg of LAAM. For four measures (the "any drug effect" VAS, agonist adjective scale, Fraser scale, and pupil diameter), the relative potency estimate was significantly greater than the 0.8:1.0 ratio used in product labeling. Additionally, for two of those measures (the Fraser scale and pupil diameter), the relative potency estimate was significantly greater than 1.0, indicating that, for those measures, LAAM was significantly more potent than methadone.

Figure 2 shows the dose-effect curves for both LAAM and methadone using the peak effect data from representative measures that yielded valid bioassays. There were clear dose-related increases for each drug on subject-rated ("like the drug"; "any drug effect"), observer-rated (magnitude of drug effect), and physiological (pupil diameter) measures. On all measures in Fig. 2, the 30- and 60-mg doses of both agonists differed significantly from placebo. In many cases, LAAM produced marginally greater effects than the same dose of methadone (see Fig. 2); this trend toward a difference between drugs at equivalent doses was especially apparent on the pupil diameter measure. There were similar trends on measures that did not meet the criteria for a valid bioassay, especially at the 30 and 60 mg doses (e.g., PCAG scale of the ARCI, observer-rated nodding, etc.; data not shown).

Naloxone Effects on Pupil Diameter 24 h After Agonist Administration

All subjects ($n = 5$) completed all scheduled 24-h postagonist naloxone challenge sessions, and data from these sessions were analyzed statistically. The effects of naloxone 24 h after each agonist dose are shown in Fig. 3, which displays averaged pupil data for all agonist conditions. Analysis of the data in Fig. 3 revealed significant main effects of agonist dose [$F(6,24) = 13.80$; $P < .001$; $\eta^2 = 0.77$] and session time [$F(13,52) = 18.90$; $P < .001$; $\eta^2 = 0.82$] and highlight four

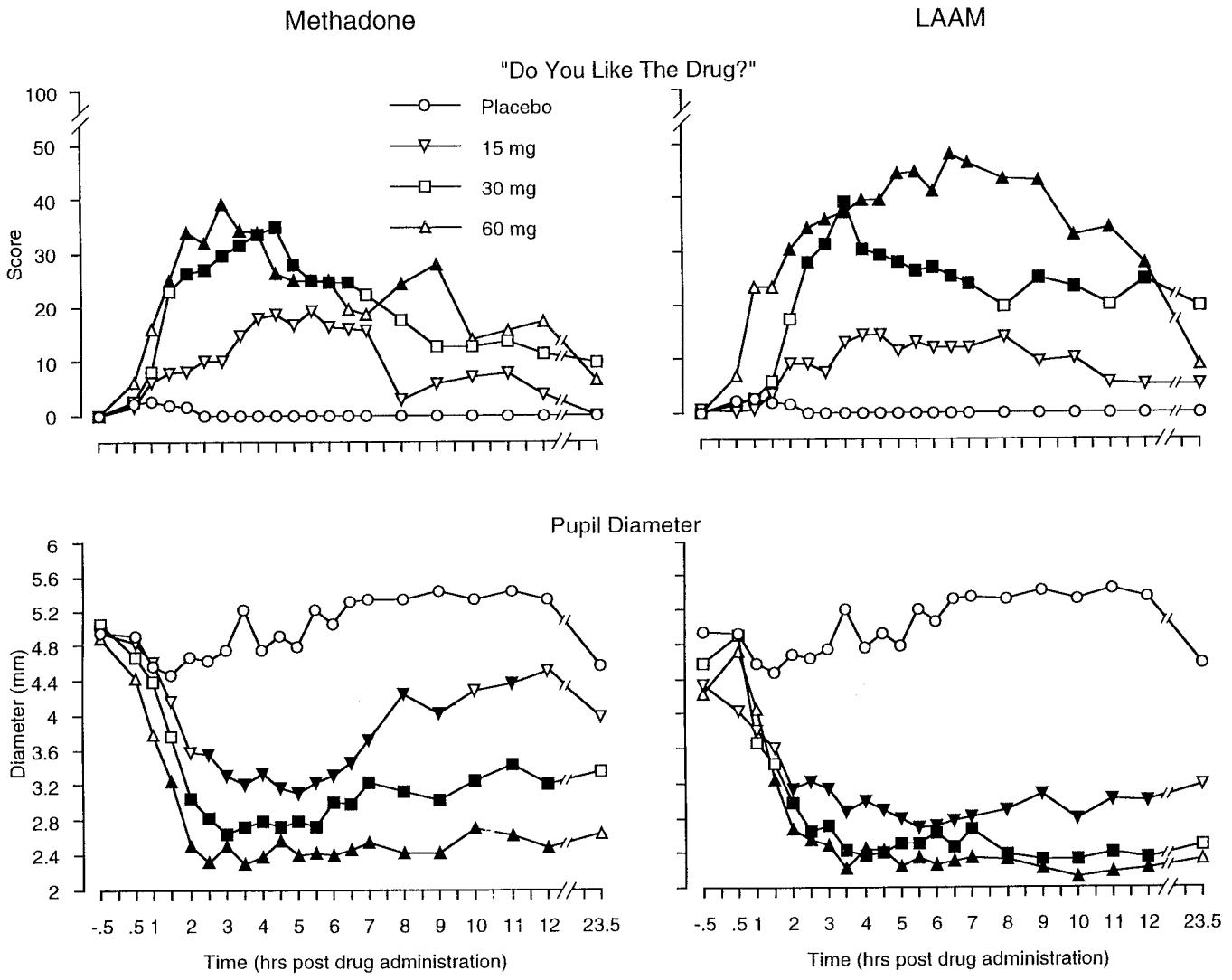

Fig. 1. Time course functions and dose effects for oral methadone (left column) and LAAM (right column) on the "Do you like the drug" VAS (top row) and pupil diameter (bottom row) measures. Data points are means of five subjects. Placebo data are reproduced in each column for clarity. Filled symbols indicate that values are significantly different from the corresponding placebo value at the same time point ($P < .05$, Tukey's post hoc tests). Data are expressed as raw scores.

important points: 1) prenaloxone values (i.e., baseline; 23.5 h after agonist administration) differed in a dose-related manner for both methadone and LAAM; 2) pupil diameter increased, relative to baseline values, after naloxone administration in all methadone and LAAM conditions; 3) the effects of 1 mg/70 kg of naloxone on pupil diameter were related inversely to LAAM and methadone dose; naloxone failed to reverse completely the pupil constriction produced by 60 mg/70 kg LAAM; and 4) for 60 mg of methadone and for all LAAM doses, significant pupil constriction apparent 24 h after agonist administration (relative to placebo) re-emerged ~90 min after naloxone administration and continued throughout the remainder of the session. This degree of pupil constriction 90 min after naloxone administration was comparable with baseline (prenaloxone) values. For 30 and 60 mg of LAAM, significant pupil constriction (relative to placebo) was also apparent 71.5 h after agonist dosing (data not shown).

The data displayed in Fig. 3 clearly indicate that, in some conditions, residual agonist effects were apparent before, during, and after the 24-h postagonist naloxone challenge. These residual agonist effects likely obscured precipitated withdrawal effects at this postagonist timepoint. Examination of data from the observer-rated measures collected in these sessions revealed that naloxone administration produced highly variable results. Naloxone administration increased ratings on some subject-rated measures (e.g., dislike the drug; bad drug effect VAS) in the 24-h challenge condition, but these increases were consistent with a reversal of the residual (positive) agonist effects that were apparent for many conditions during baseline assessment (i.e., 23.5 h after the agonist dose). Thus, any potential precipitated withdrawal effects at the 24-h postagonist interval were confounded by continued agonist action.

Discussion

This clinical study compared the acute agonist effects produced by LAAM or methadone in a within-subject design; the study also examined the ability of naloxone to reverse those

TABLE 2
Results of peak effect analyses for agonist-sensitive measures from the seven relative potency assessment sessions

Measure	Condition Effects[a]		Dose Effect[b]		Relative Potency[c]	
	$F_{(6,24)}$	P	Meth	LAAM	Estimate	95% CI
Subject-rated						
VAS						
High	10.02	<.001	↑	↟	1.20	0.75–2.07
Any drug effect	10.36	<.001	↑	↟	1.27*	0.84–2.04
Good effects	8.70	<.001	↑	↟	1.18	0.71–2.10
Like	7.49	<.001	↑	↟	1.21	0.69–2.36
Desire opiates	2.85	<.05		↑	N/A[d]	N/A
Adjective scales						
Agonist effects	8.39	<.05	↟	↑	1.85*	0.94–7.23
Fraser scale	8.35	<.004	↑	↟	2.11**	1.21–5.84
ARCI						
Amphetamine	1.53	N.S.				
Benzedrine	1.57	N.S.				
MBG	4.93	<.003				
PCAG	9.22	<.001	↑	↟	N/A	N/A
LSD	2.17	N.S.				
Observer-rated items						
Nodding	3.46	<.05	↑	↑	N/A	N/A
Scratchy	3.26	<.05	↑	↑	N/A	N/A
Magnitude of drug effect	10.79	<.001	↑	↟	N/A	N/A
Restlessness	1.95	N.S.				
Talkative	2.28	N.S.				
Sleepy/sedated	1.78	N.S.				
Energetic	1.14	N.S.				
Irritable	1.00	N.S.				
Friendly	1.50	N.S.				
Vomiting	1.62	N.S.				
Drunken	2.98	<.06		↟	N/A	N/A
Nervous	<1.0	N.S.				
Physiological						
Pupil diameter	10.57	<.005	↓	↓	1.63**	1.07–2.91
Heart rate[e]	<1.0	N.S.				
Skin temperature[e]	1.50	N.S.				
Systolic blood pressure[e]	2.17	N.S.				
Diastolic blood pressure[e]	1.03	N.S.				

[a] Condition effects may be due to the effects of either LAAM or methadone.
[b] ↟ Significant ($P < .05$) difference between 15- and 60-mg doses; ↑ nonsignificant increases between doses, where the effects of 60 > 30 > 15 mg.
[c] Relative potency expressed as milligrams of methadone necessary to produce the same effect as 1 mg of LAAM.
[d] N/A, data did not meet one or more of the criteria for a valid bioassay. N.S., not significant.
[e] Because of computer error, heart rate, temperature, and blood pressure data for subject 3 were lost. Analyses of these measures are based on the remaining four subjects' data [df, (6, 18)].
* Significant difference from the reported 0.8 relative potency estimate; ** significant difference from 1.0.

effects. Analysis of agonist effects suggests that LAAM may be more potent than methadone; an accurate methadone:LAAM relative potency estimate is approximately 1.4:1.0 (Table 2). Current product labeling referring to a 0.8:1.0 methadone:LAAM relative potency ratio likely underestimates the potency of LAAM.

In contrast to the current results, preclinical studies indicate that LAAM is less potent than methadone, although the metabolites of LAAM are more potent (e.g., Vaupel and Jasinski, 1997). Relative to methadone, nor-LAAM is approximately 5 to 10 times more potent, whereas dinor-LAAM is approximately 1 to 4 times more potent (e.g., Brandt et al., 1997; Vaupel and Jasinski, 1997). These findings suggest that including the effects of LAAM's metabolites in relative potency determinations, for instance by using a sufficient measurement interval, may provide a more complete estimate of the effects of LAAM administration. In the current study, relative potency estimates were based on data collected for 12 h after agonist administration. This 12-h measurement interval includes the period when plasma levels of the active metabolites of LAAM have peaked (e.g., Billings et al., 1973, 1974; Henderson et al., 1977; Walsh et al., 1998). Another clinical study used a similar measurement interval and reported similar results; an acute 40-mg LAAM dose produced greater pupil constriction than did 40 mg of methadone (Fraser et al., 1954). Discrepancies between preclinical and clinical methadone:LAAM relative potency estimate results may be due to shorter (i.e., 5-h) measurement intervals used in preclinical studies.

One reason to consider metabolite effects when determining therapeutic dose is that they may lead to overmedication (e.g., Henderson et al., 1977). Overmedication may influence the response of treatment-seeking heroin users during LAAM induction when doses are progressively increasing (Ling et al., 1976; Jones et al., 1998). If induction doses underestimate the effects of LAAM, some patients may leave treatment due to unexpectedly strong agonist effects. Attrition during induction has been a concern in the development of LAAM. In several clinical trials using LAAM induction schedules that were based upon methadone experience,

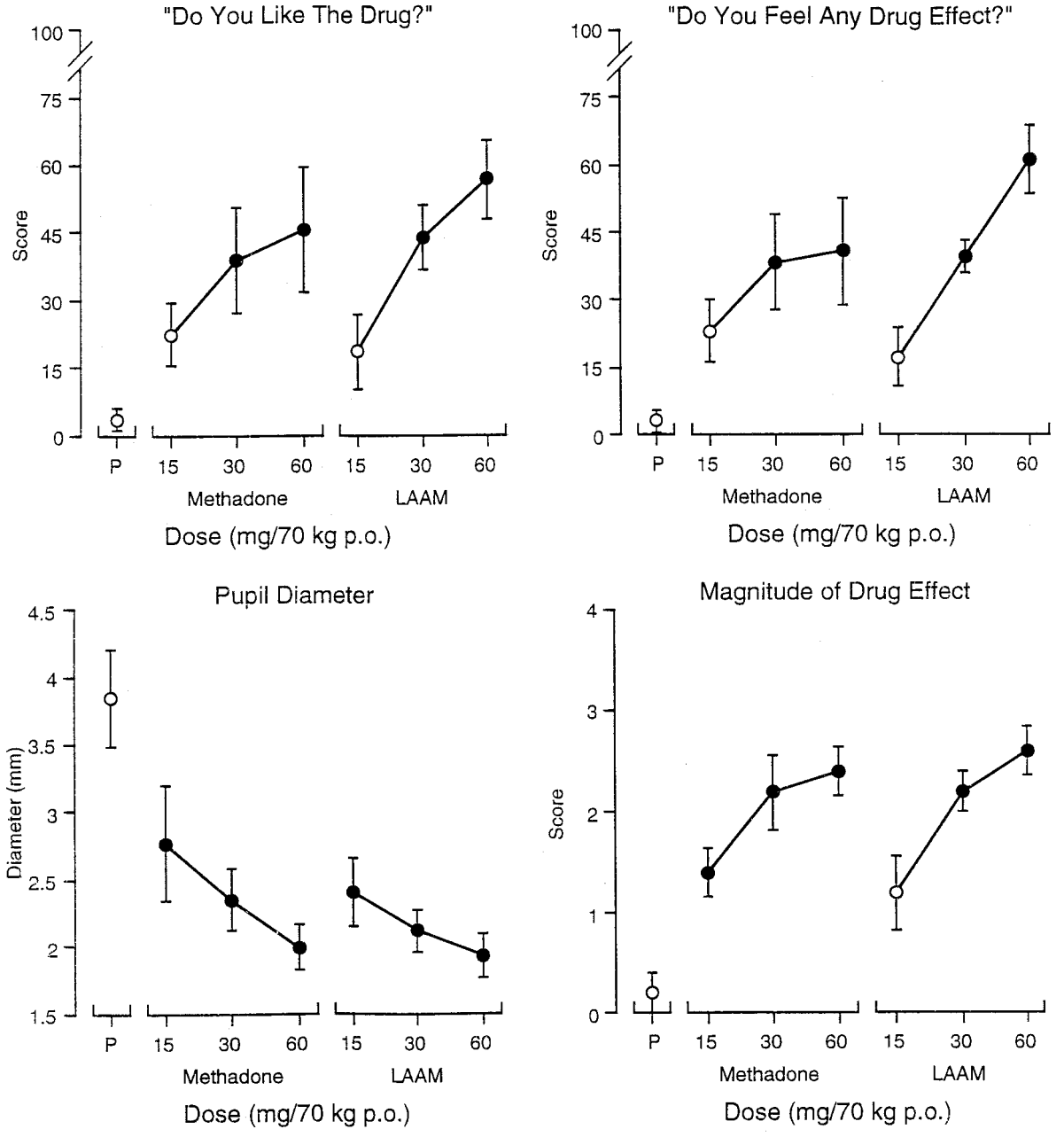

Fig. 2. Dose effects based on peak effect data for oral methadone and LAAM on four measures. The measures are the "Do you like the drug" VAS, "Do you feel any drug effect" VAS, pupil diameter, and observer-rated magnitude of drug effect. "P" designates placebo values. Data points are means ± S.E.M. for five subjects. Filled symbols indicate a significant difference from placebo ($P < .05$, Tukey's post hoc tests).

trends toward a greater than expected dropout rate for LAAM-treated subjects were observed (Ling et al., 1976; Senay et al., 1977). Similarly, in a LAAM dose comparison study where LAAM doses were chosen using the 0.8:1.0 methadone:LAAM relative potency ratio, there was a trend toward greater attrition in the high-dose condition during induction, and agonist side effects were cited as a primary reason for dropout in that condition (Jones et al., 1998). If a 1.4:1.0 relative potency estimate were used during LAAM induction, attrition due to overmedication may decrease, potentially increasing the treatment efficacy of LAAM.

These results also provided a within-study comparison of the pharmacodynamic profile of LAAM and methadone. The onset of agonist effects was similar for the two medications (1–2 h), whereas the time to peak effect and duration of action were both greater for LAAM. These comparative pharmacodynamic data are consistent with previous results from separate studies (e.g., Fraser et al., 1954; Martin et al., 1973; Walsh et al., 1995, 1998) and suggest that patients can expect to experience methadone-like agonist effects as quickly after LAAM as they would after methadone. However, peak LAAM agonist effects, which may exceed those of the same dose of methadone, will not be apparent until 4 to 7 h after dosing.

Another feature of the pharmacodynamic profile of the agonist effects of LAAM was observed when naloxone was administered at the 24-h postagonist interval (Fig. 3): 1) unlike with 60 mg of methadone, naloxone (1 mg/70 kg i.m.)

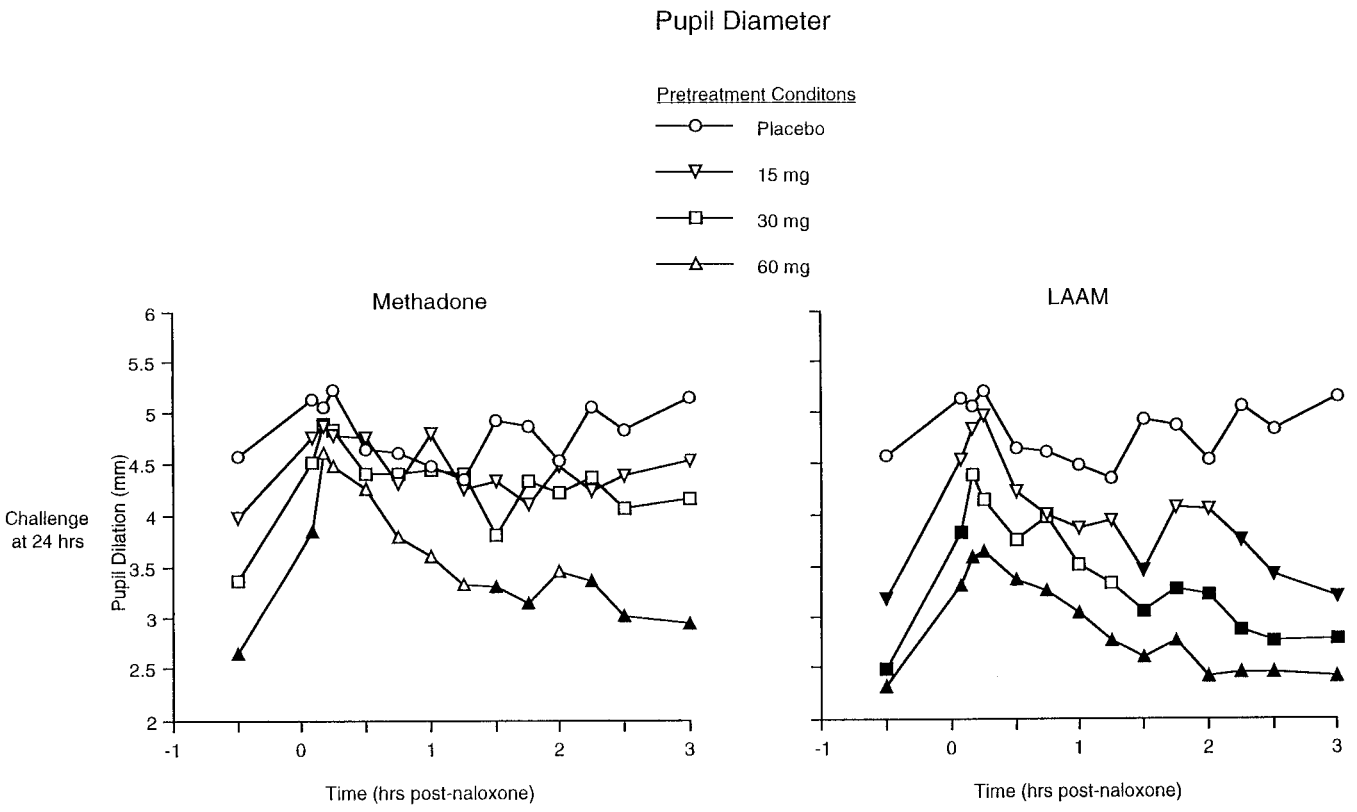

Fig. 3. Time course of pupil diameter changes after i.m. naloxone (1 mg/70 kg) 24 h after doses of placebo and oral methadone (left) and LAAM (right). In all other details, the figure is similar to Fig. 1.

was unable to reverse fully the effects of 60 mg of LAAM; pupil diameter increased but remained significantly constricted. This failure of naloxone to reverse completely the effects of 60 mg of LAAM demonstrates the greater efficacy of LAAM on this physiological measure and suggests that LAAM overdose may require relatively high-dose antagonist treatment; and 2) for every dose of LAAM tested, significant pupil constriction re-emerged ~90 min after naloxone administration, consistent with the half-life of naloxone. This re-emergence of an agonist effect in each LAAM dose condition after naloxone administration (also apparent in the 60-mg methadone condition) demonstrates the long duration of the effects of LAAM and highlights the influence of LAAM's long-acting metabolites. A long-acting antagonist such as nalmefene (e.g., Kaplan and Marx, 1993) or a continuous infusion of naloxone (e.g., Bradberry and Raebel, 1981) may be indicated in treatment of acute LAAM overdose.

Study Limitations

Limitations of the current study include its small sample and acute administration procedures. Five subjects completed the relative potency determination sessions, although nine subjects were enrolled into this study. Despite the small sample size, the study was remarkably powerful; of the measures in Table 2 that attained statistical significance, power ranged from 0.78 to 0.99. This high degree of power attained with a small sample is due to the within-subject design used and large effect sizes observed (i.e., $0.42 < \eta^2 < 0.73$). Thus, although the reported sample size was modest, the results, demonstrating LAAM's greater than expected potency, were robust. Moreover, the three subjects who failed to complete the protocol due to clinically significant respiratory depression after receiving 60 mg of LAAM also highlight LAAM's greater than expected potency. Including more subjects in this study would have exposed other volunteers to unnecessary medical risks to support a conclusion that was already statistically and clinically supported; LAAM is more potent than believed previously.

A relative potency estimate of LAAM and methadone based upon the effects of acute doses may differ from one based on the effects of maintenance treatment. Factors that might effect a relative potency estimate based on maintenance doses include potential differential tolerance for LAAM and methadone and/or a reduction in efficacy across the dosing interval (i.e., 24 h with methadone, 72 h with LAAM). Moreover, the measures used in this acute dosing study may not be wholly relevant to maintenance treatment, where withdrawal suppression and opioid blockade are of primary importance (e.g., Kreek, 1992). Thus, future studies aimed at determining the relative potency of the two drugs during maintenance would be valuable.

Summary

Under the acute dosing conditions of this study, LAAM was not less potent than methadone and may, in fact, be more potent. These observations suggest that product labeling underestimates LAAM's potency relative to methadone. Underestimating LAAM's potency could explain greater than expected attrition rates during induction onto LAAM maintenance treatment (e.g., Jones et al., 1998) and suggests caution during LAAM induction for patients whose level of opioid tolerance is indeterminate. Moreover, LAAM's po-

tency, long duration of action, active metabolites, and the re-emergence of agonist effects after naloxone administration observed in this study all suggest that LAAM overdose may be best treated with long-acting opioid antagonists or multiple doses of shorter-acting opioid antagonists.

Acknowledgments

We thank Dr. David Ginn and the staff of the residential research unit for excellent medical support.

References

Bickel WK, Stitzer ML, Liebson IA and Bigelow GE (1988) Acute physical dependence in man: Effects of naloxone after brief morphine exposure. *J Pharmacol Exp Ther* **244:**126–132.

Billings RE, Booher R, Smits S, Pohland A and McMahon RE (1973) Metabolism of acetylmethadol: A sensitive assay for noracetylmethadol and the identification of a new active metabolite. *J Med Chem* **16:**305–306.

Billings RE, McMahon RE and Blake DA (1974) *L*-Acetylmethadol (LAM) treatment of opiate dependence: Plasma and urine levels of two pharmacologically active metabolites. *Life Sci* **14:**1437–1446.

Bradberry JC and Raebel MA (1981) Continuous infusion of naloxone in the treatment of narcotic overdose. *Drug Intell Clin Pharmacol* **15:**945–950.

Brandt MR, Cabansag SR and France CP (1997) Discriminative stimulus effects of *L*-α-acetylmethadol (LAAM), buprenorphine, and methadone in morphine-treated rhesus monkeys. *J Pharmacol Exp Ther* **282:**574–584.

Dole VP and Nyswander MA (1965) A medical treatment for diacetylmorphine (heroin) addiction. *J Am Med Asoc* **193:**80–84.

Eissenberg T, Greenwald MK, Johnson RE, Liebson IA, Bigelow GE and Stitzer ML (1996) Buprenorphine's physical dependence potential: Antagonist-precipitated withdrawal in humans. *J Pharmacol Exp Ther* **276:**449–459.

Ellenhorn MJ, Schonwald S and Wasserberger J (1997) *Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning,* Williams & Wilkins, Baltimore.

Finney DJ (1978) *Statistical Method in Biological Assay,* MacMillan, New York.

First MB, Spitzer RL, Gibbon M and Williams JBW (1994) *Structured Clinical Interview for DSM-IV Axis Disorders - PATIENT EDITION* (SCID-I/P Version 20), New York State Psychiatric Institute Biometrics Research, New York.

Fraser HF and Isbell H (1952) Actions and addiction liabilities of alpha-acetylmethadols in man. *J Pharmacol Exp Ther* **105:**458–465.

Fraser HF, Nash TL, Vanhorn GD and Isbell H (1954) Use of miotic effect in evaluating analgesic drugs in man. *Arch Int Pharmacodynam Ther* **98:**443–451.

Greenwald MK, June HL, Stitzer ML and Marco AP (1996) Comparative clinical pharmacology of short-acting mu opioids in drug abusers. *J Pharmacol Exp Ther* **277:**1228–1236.

Haertzen CA (1974) *An Overview of Addiction Research Center inventory Scales (ARCI): An Appendix and Manual of Scales* (DHEW Publication No (ADM) 74–92), National Institute on Drug Abuse, Rockville MD.

Henderson GL, Weinberg JA, Hargreaves WA, Lau DHM, Tyler J and Baker B (1977) Accumulation of *L*-α-acetylmethadol [LAAM] and active metabolites in plasma following chronic administration. *J Anal Toxicol* **1:**1–5.

Higgins ST, Preston KL, Cone EJ, Henningfield JE and Jaffe JH (1992) Supersensitivity to naloxone following acute morphine pretreatment in humans: Behavioral hormonal and physiological effects. *Drug Alcohol Depend* **30:**13–26.

Himmelsbach CK (1941) The morphine abstinence syndrome: Its nature and treatment. *Ann Int Med* **15:**829–839.

Jaffe JH, Schuster CR, Smith BB and Blachley PH (1970) Comparison of acetylmethadol and methadone in the treatment of long-term heroin users. *J Am Med Assoc* **211:**1834–1836.

Jaffe JH and Senay EC (1971) Methadone and *L*-methadylacetate: Use in management of narcotics addicts. *J Am Med Assoc* **216:**1303–1305.

Jones B and Kenward MG (1989) *Design and Analysis of Cross-Over Trials,* Chapman and Hall, London.

Jones HE, Strain EC, Bigelow GE, Walsh SL, Stitzer ML, Eissenberg T and Johnson RE (1998) Induction onto LAAM: Safety and efficacy. *Arch Gen Psychiatry* **55:**729–736.

Kaplan JL and Marx JA (1993) Effectiveness and safety of intravenous nalmefene for emergency department patients with suspected narcotic overdose: A pilot study. *Ann Emerg Med* **22:**187–190.

Kreek MJ (1992) Rationale for maintenance pharmacotherapy of opiate dependence, in: *Addictive States* (O'Brien CP and Jaffe JH eds) pp 205–230, Raven Press Ltd, New York.

Ling W, Charuvastra VC, Kaim SC and Klett CJ (1976) Methadyl acetate and methadone as maintenance treatments for heroin addicts. *Arch Gen Psychiatry* **33:**709–720.

Ling W, Klett CJ and Gillis RD (1978) A cooperative clinical study of methadyl acetate I. Three-times-a-week regimen. *Arch Gen Psychiatry* **35:**345–353.

Martin WR, Jasinski DR, Haertzen CA, Kay DC, Jones BE, Mansky PA and Carpenter RW (1973) Methadone –A reevaluation. *Arch Gen Psychiatry* **28:**286–295.

Martin WR, Sloan BS, Sapira JD and Jasinski DR (1971) Physiologic, subjective and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine and methylphenidate in man. *Clin Pharmacol Ther* **12:**245–258.

McMahon RE, Culp HW and Marshall FJ (1965) The metabolism of α-*dl*-acetylmethadol in the rat: The identification of the probable active metabolite. *J Pharmacol Exp Ther* **149:**436–445.

Medical Economics Data (1998). *Physician's Desk Reference,* Medical Economics Data Production Company, Montvale, NJ.

Nutt JG and Jasinski DR (1974) Methadone-naloxone mixtures for use in methadone maintenance programs. *Clin Pharmacol Ther* **15:**156–166.

Schuh KJ, Walsh SL, Bigelow GE, Preston KL and Stitzer ML (1996) Buprenorphine morphine and naloxone effects during ascending morphine maintenance in humans. *J Pharmacol Exp Ther* **278:**836–846 .

Senay EC, Dorus W and Renault PF (1977) Methadyl acetate and methadone: An open comparison. *J Am Med Assoc* **237:**138–142.

Stitzer ML, Wright C, Bigelow GE, June HL and Felch LJ (1991) Time course of naloxone-precipitated withdrawal after acute methadone exposure in humans. *Drug Alcohol Depend* **29:**39–46.

Vaupel DB and Jasinski DR (1997) *l*-α-acetylmethadol, *l*-α-acetyl-*N*-normethadol, and *L*-α-acetyl-*N,N*-dinormethadol: Comparisons with morphine and methadone in suppression of the opioid withdrawal syndrome in the dog. *J Pharmacol Exp Ther* **283:**833–842.

Walsh SL, Johnson RE, Cone EJ and Bigelow GE (1998) Intravenous and oral *l*-alpha-acetylmethadol: Pharmacodynamics and pharmacokinetics in humans. *J Pharmacol Exp Ther* **285:**71–82.

Walsh SL, Preston KL, Bigelow GE and Stitzer ML (1995) Acute administration of buprenorphine in humans: Partial agonist and blockade effects. *J Pharmacol Exp Ther* **247:**361–372.

Walsh SL, Preston KL, Stitzer ML, Cone E and Bigelow GE (1994) Clinical pharmacology of buprenorphine: Ceiling effects at high doses. *Clin Pharm Exp Ther* **55:**569–580.

Wright C, Bigelow GE, Stitzer ML and Liebson IA (1991) Acute physical dependence in humans: Repeated naloxone-precipitated withdrawal after a single dose of methadone. *Drug Alcohol Depend* **27:**139–148.

Zaks A, Fink M and Freedman AM (1972) Levomethadyl in maintenance treatment of opiate dependence. *J Am Med Assoc* **220:**811–813.

Send reprint requests to: Thomas Eissenberg, Ph.D., Department of Psychology and Institute for Drug and Alcohol Studies, Virginia Commonwealth University, Box 980205, Richmond, VA. E-mail: teissenb@vcu.edu