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Intravenous and Oral *l*-α-Acetylmethadol: Pharmacodynamics and Pharmacokinetics in Humans[1]

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ABSTRACT

Levo-α-acetylmethadol (LAAM) is a long-acting opioid agonist approved for use as a maintenance treatment for opioid dependence. Previous clinical studies report that the onset of the effects of LAAM is slower after parenteral administration than oral administration; however, preclinical studies suggest otherwise. This study examined the pharmacodynamic and pharmacokinetic profile of LAAM when given orally and intravenously to humans. Opioid-experienced volunteers ($n = 6$), who were not physically dependent on opioids, received LAAM (20 and 40 mg/70 kg i.v. and p.o.) and placebo under double-blind, double-dummy conditions during five weekly experimental sessions. Behavioral, physiological, subjective and pharmacokinetic measures were collected before and for 96 hr after drug administration. Intravenous LAAM produced significant subjective and physiological effects that appeared within 5 min, whereas the effects of oral LAAM appeared more slowly within 1 to 2 hr after drug administration. Pharmacokinetic data indicate that the immediate effects of intravenous LAAM are largely attributable to the parent drug rather than the active metabolites, nor-LAAM and dinor-LAAM. LAAM produced prototypic opioid agonist effects (*i.e.,* miosis, subjective ratings of high, nodding) that were of equal magnitude across routes, dose-related and of long duration (up to 60 hr). These data are in contrast to previous clinical reports and indicate that LAAM produces effects of immediate onset when administered parenterally, which suggests that intravenous LAAM possesses greater abuse potential than previously believed.

Levo-α-acetylmethadol is a synthetic opioid that was approved for use as a treatment for opioid dependence by the Food and Drug Administration in 1993. A congener of methadone, LAAM produces opioid effects typical of *mu* agonists, including analgesia, euphoria, miosis and respiratory depression (Fraser and Isbell, 1952; David and Semler, 1952). Compared with other *mu* opioid agonists, LAAM has an exceptionally long duration of action and can produce effects lasting up to 72 hr after a single acute dose (Fraser and Isbell, 1952). This long duration of action has enabled clinicians to administer LAAM to opioid-dependent patients with less-than-daily dosing schedules and to achieve adequate suppression of withdrawal symptoms when administering LAAM as infrequently as three times weekly (Ling *et al.*, 1975; 1976; Senay *et al.*, 1977; Freedman and Czertko, 1981).

The persistent action of LAAM has been attributed primarily to its sequential N-demethylation to two primary active metabolites, nor-LAAM and dinor-LAAM (McMahon *et al.*, 1965; Billings *et al.*, 1973, 1974; Henderson *et al.*, 1977a). Although N-demethylation by cytochrome P450 3A4 apparently serves as the primary metabolic path (Moody *et al.*, in press), LAAM may also be deacetylated to form methadol and normethadol (see Kaiko and Inturrisi, 1975; Chiang *et al.*, 1995). norLAAM and dinorLAAM are present in plasma for up to 72 to 96 hr after acute or chronic dosing with LAAM in animals (Henderson *et al.*, 1977a) and humans (Kaiko and Inturrisi, 1975; Henderson *et al.*, 1977b), whereas the parent drug is no longer detected. Although LAAM has a half-life estimated to range from 4.6 to 7 hr, the half-lives of nor-LAAM and dinor-LAAM are estimated to range up to 48 hr and 4 or more days, respectively (Henderson *et al.*, 1977c; Kaiko and Inturrisi, 1975; Chiang *et al.*, 1995). Reports suggest that nor-LAAM is 5 to 10 times more potent than LAAM and dinor-LAAM in a variety of assays (Nickander *et al.*, 1974; Billings *et al.*, 1973; Perez-Reyes, 1985). Thus, the potency and long duration of action of LAAM has been attributed, in large part, to these long-acting active metabolites.

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ABBREVIATIONS: AUC, area under the curve; LAAM, *l*-α-acetylmethadol; ARCI, Addiction Research Center Inventory; ANOVA, analysis of variance; BENZ, benzedrine scale; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders (3rd edition, revised); LSD, lysergic acid diethylamide ("dysphoria" scale); MBG, morphine-benzedrine group ("euphoria" scale); PCAG, pentobarbital-chlorpromazine-alcohol group ("sedation" scale); S.E.M., standard error of the mean.

The earliest clinical studies of LAAM reported the unusual finding that the effects of LAAM administered parenterally were delayed in onset in comparison with those of orally administered LAAM. Oral administration of LAAM at doses of 30 to 40 mg produced measurable effects within 1 hr, whereas detectable opioid effects were not observed until up to 4 to 6 hr after intravenous or subcutaneous LAAM at 10 to 30 mg (Fraser and Isbell, 1952; Fraser *et al.*, 1954). This finding is antithetical to the predicted relationship between the rate of drug delivery and the onset of pharmacodynamic effects; typically the onset of drug action is fastest after administration by a parenteral route (*e.g.,* Benet *et al.*, 1991). To explain this atypical finding, it was hypothesized that the parent drug LAAM was inactive and that the parenteral delivery of the drug slowed the rate of metabolism and formation of the active metabolites. Statements characterizing LAAM as an inert prodrug and descriptions of its delayed parenteral effects have been included in widely used pharmacology texts (*e.g.,* see Jaffe and Martin, 1991; Jaffe, 1992). These data also contributed to regulatory decisions that restricted take-home doses of LAAM because of the presumed risk of toxic interactions between supplemental illicit opiates used after oral LAAM.

In contrast to the widely cited report by Fraser and Isbell in 1952, another clinical study on LAAM published in the same year went relatively unnoticed (Keats and Beecher, 1952). In that study the analgesic efficacy of LAAM was evaluated in postsurgical patients who received acute doses of LAAM subcutaneously. LAAM (5–20 mg) was modestly effective at producing analgesia. Importantly, there was no significant delay in the analgesic response in contrast to the delayed "euphoric" response observed by Fraser and Isbell (1952). Conflicting findings regarding the differential latency of the onset of parenteral *versus* oral LAAM also have been reported in laboratory animals. Studies in monkeys and dogs have reported that the time to onset of effects for intravenous and intramuscular LAAM is similar to that of oral LAAM (*i.e.,* 30 min to 1 hr post-drug administration) on various dependent measures including analgesia, sedation and electroencephalographic effects (Henderson, 1976a; Killam, 1976; Lukas *et al.*, 1980; see also Archer, 1976). In another study, the relative analgesic potencies of LAAM, nor-LAAM and dinor-LAAM were compared with the mouse writhing assay (Smits, 1974). The analgesic effects of LAAM were apparent within 1 hr after subcutaneous administration, although the response to LAAM was somewhat slower than that of nor-LAAM or dinor-LAAM. Similarly, LAAM was pharmacologically active, although less potent, than nor-LAAM and dinor-LAAM in the guinea pig ileum twitch assay (Nickander *et al.*, 1974). In this case, use of an isolated tissue preparation precluded appreciable biotransformation of LAAM to its active metabolites. These studies suggest that the parent drug LAAM is an active drug and that LAAM can produce effects shortly after parenteral administration which are not caused by its metabolic transformation to nor-LAAM and dinor-LAAM.

In summary, there are conflicting findings from studies evaluating the relative time to onset of the effects of parenteral and oral LAAM. The early clinical studies cited herein were published largely as descriptive case reports and were conducted before the development of rigorously controlled, double-blind laboratory procedures and the use of standardized subjective and objective rating measures. To date, there have been no contemporary studies assessing the pharmacodynamic and pharmacokinetic profiles of oral and parenteral LAAM in humans. Because of the discrepancies between prior reports regarding the onset of parenteral LAAM effects, the present laboratory study was undertaken to reevaluate the effects of LAAM in humans. This study was designed to characterize and compare the acute pharmacodynamic and pharmacokinetic profiles of LAAM when administered by the intravenous and the oral routes to opioid-experienced human volunteers. The objectives were 1) to characterize the pharmacodynamic profile including the time to onset, duration of action and magnitude of effects and 2) to characterize the pharmacokinetic disposition of LAAM and its metabolites in plasma after administration by the oral and intravenous routes.

Methods

Subjects

The participants were healthy adult male volunteers recruited through newspaper advertisements and word of mouth. All volunteers were current intravenous users of opiates, but were not physically dependent on opioids or on any drugs except nicotine and currently were not seeking treatment for substance abuse or dependence. Physical dependence was assessed by interview and examination, and by extended observation in a drug-free environment before study participation. Volunteers received a medical screening examination which included hematology, blood chemistries, urinalysis, assessment for adequate venous access and an electrocardiogram. Psychological assessments were conducted with the Structured Clinical Interview (SCID-II) (Spitzer and Williams, 1986), and subjects diagnosed with any Axis I disorder other than substance abuse or dependence were excluded.

Nine subjects were enrolled in the study, but three were discharged before completion of the study. One was discharged after experiencing a wheal and flare reaction at the site of intravenous infusion of LAAM, and two were discharged because their self-reports were inconsistent with observable signs of drug effects. Six subjects completed the study. All were black males, age 28 to 46 years (mean, 37.3 years). They reported an average of 12 years education (range, 11–14 years). All subjects met the DSM-III-R diagnostic criteria for an opiate use disorder ($n = 5$ for dependence; $n = 1$ for abuse) and for cocaine dependence. The group reported an average of 16.7 years of heroin use (range, 4–28) and reported using heroin approximately 15 of the past 30 days (range, 6–26). This study was approved by the local Institutional Review Board; subjects gave their written informed consent and were paid for their participation.

Setting/General Procedure

The study was completed while subjects resided on a closed 14-bed research unit that was described previously (Walsh *et al.*, 1995). This facility is staffed by licensed nursing personnel 24 hr/day and is used exclusively for behavioral pharmacology research. Subjects were required to adhere to written program rules and protocol restrictions (*i.e.*, dietary, sleep hours, etc.). Recreational activities were provided including exercise equipment, arts and crafts projects, television and video games. Urine specimens were collected daily and randomly tested for evidence of illicit drugs on an EMIT system (Behring Diagnostics, San Jose, CA) and/or using thin-layer chromatography to ensure the absence of drugs other than those administered experimentally. Breath alcohol tests also were given to the subjects on admission and at weekly intervals. Breathalyzer tests were negative for alcohol, and no illicit drug use was found in any subject during the study. Subjects were maintained on a caffeine-free diet. Five of

the six subjects were cigarette smokers; they were allowed free access to cigarettes except for during and 1 hr preceding each experimental session.

Experimental Design

All subjects received a single screening dose of LAAM (10 mg) given intravenously during the first week of the study. The purpose of this screening dose was to assess for any idiosyncratic reaction to the intravenous infusion or for unusual sensitivity to LAAM. This drug administration was single-blind, plasma samples were not collected and data from this session were not included in any analyses.

A double-blind, double-dummy crossover design was used to evaluate the effects of oral and intravenous LAAM. For the double-dummy control, subjects received both an oral and an intravenous preparation on each study day, but staff and subject were unaware of which, if either, was active. The oral solution was administered immediately before the intravenous solution. Subjects were tested once weekly with one of the following doses: placebo, oral LAAM (20 and 40 mg/70 kg b.wt.) and intravenous LAAM (20 and 40 mg/70 kg). There were at least 7 days between each experimental session. Doses were administered with a constrained randomized order; the constraint was that administration of the lower intravenous dose always preceded the higher intravenous dose. Subjects, nursing staff and technical staff involved in data collection were blind to the dosing schedule.

Drugs

An oral LAAM HCl solution was obtained from the Research Triangle Institute through the Chemistry and Pharmaceutics Branch, National Institute on Drug Abuse (Rockville, MD). The stock solution was a 10 mg/ml concentration. All oral LAAM doses were prepared by adding an additional volume of a sugar- and alcohol-free flavored syrup (Ora-Sweet SF, Paddock Laboratories, Inc., Minneapolis, MN) diluted with water (1:4) that contained 12 ng/ml denatonium benzoate (Bitrex, JH Walker and Company, Inc., Mt. Vernon, NY) as a bitter taste-mask for a final dose volume of 20 ml. The same volume of diluted Ora-Sweet solution with Bitrex served as the oral placebo solution.

Intravenous solutions of LAAM HCl were prepared from bulk powder manufactured through Orpharm, Inc. (Houston, TX) and supplied through BioDevelopment Corporation (McLean, VA). LAAM HCl was weighed and dissolved in the appropriate amount of sterile water for injection (Abbott Laboratories, North Chicago, IL) for a total delivery volume of 2 ml. Solutions were prepared aseptically under a laminar flow hood and filtered through a 0.22-μm-pore-size filter (Millipore Products Division, Bedford, MA) into a sterile pyrogen-free vial. Placebo infusions consisted of saline for injection USP (Fjisawa USA, Inc., Deerfield, IL). All intravenous doses were in a volume of 2 ml delivered through a venous catheter over 1 min by a staff physician.

Experimental Sessions

Subjects were fasted from midnight preceding each of the five experimental sessions. Intravenous catheters were inserted into each arm within an hour before the start of the session; one was used for drug administration and the other for collection of blood samples. A slow-drip intravenous line was kept in place during the experimental session only. The subjects were escorted from the residential unit to the experimental session room at approximately 8:30 A.M. The subject was seated in a cushioned chair directly in front of a Macintosh computer which was used to collect data. The computer recorded physiological measures (except pupil diameter) and presented all questionnaires in the appropriate order. Physiological measures (except for pupil diameter) were collected by an automatic physiologic monitor (Noninvasive Patient Monitor model 506, Criticare Systems, Waukesha, WI) that was interfaced with the computer. Subjects entered their questionnaire responses by use of a keyboard. A research assistant, who was blind to the treatment, was seated behind the computer with a keyboard available to initiate tasks and to enter observer-rated measures. Data printouts were collected after each session, and the data were transferred electronically to spreadsheets for analyses.

Physiological measures. The subjects were monitored continuously throughout each session. Data collection began 30 min before drug administration and continued for 8 hr after drug administration. Oxygen saturation, heart rate, skin temperature and systolic and diastolic pressure were collected every 3 min during the session. Pupil diameter was determined from photographs taken in constant ambient room lighting using a Polaroid camera (Polaroid Corp., Cambridge, MA) with a 2× magnification; photos were taken at 30 min before, at 5 and 15 min after drug administration and at 15-min intervals thereafter for the duration of the 8-hr session. Respiratory rate was measured manually by counting the number of breaths per minute at baseline and once every 15 min throughout the 8-hr session.

Subject-rated measures. During the experimental sessions, subjects responded to three computerized questionnaires: the Visual Analog Questionnaire, the Adjective Rating Questionnaire and the short form of the Addiction Research Center Inventory (Martin *et al.*, 1971). For the Visual Analog Questionnaire, the subject rated "Do you feel any DRUG EFFECT?," "How HIGH are you?," "Does the drug have any GOOD EFFECTS?," "Does the drug have any BAD EFFECTS?," "Do you LIKE the drug?," "Does the drug make you feel SICK?," and "How much do you desire OPIATES now?" by positioning the 1-mm cursor along a 100-point line marked at either end with "not at all" or "extremely." These seven visual analogs were rated 30 min before, 5 and 15 min after drug administration and at 15-min intervals thereafter for the duration of the session.

The short form of the ARCI consisted of 49 true/false questions and contained five major subscales: MBG (an index of euphoria); PCAG (an index of sedation); LSD (an index of somatic and dysphoric changes); and BENZ and AMPH scales (empirically derived amphetamine sensitive scales). The adjective rating scales were presented as 5-point scales where 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, and 4 = extremely. The subjects rated their responses to 38 adjectives from scores that were later derived for the following scales: I) the Opiate Agonist Scale (scores are summed): nodding, heavy or sluggish feeling, dry mouth, carefree, good mood, energetic, turning of stomach, skin itchy, relaxed, coasting, talkative, pleasant sick, drive, drunken, friendly, and nervous; II) the Fraser Scale (items with affirmative scores [1, 2, 3 or 4] are weighted according to the number in parentheses): turning of stomach (1), skin itchy (2), relaxed (1), coasting (2), soapbox (1), pleasant sick (1), drive (2), sleepy (2), drunken (1), and nervous (1); and III) a Withdrawal Scale (scores are summed): muscle cramps, flushing, painful joints, yawning, runny nose, chills or gooseflesh, sick to stomach, sneezing, abdominal cramps, irritable, backache, tense and jittery, sweating, depressed/sad, sleepy, shaky hands, hot or cold flashes, bothered by noises and skin clammy and damp (Preston *et al.*, 1988). The ARCI and adjective rating scales were completed 30 min before and at 30-min intervals after drug administration for the duration of the 8-hr session.

Observer-rated measures. Observer ratings were completed by a research assistant who rated the subject on a 5-point scale from 0 (not at all) to 4 (extremely) with the same adjective rating list that the subjects completed. Observers made their ratings based on observation and on spontaneous comments by the subjects. Observer ratings were completed 30 min before and at 30-min intervals after drug administration for the duration of the 8-hr session.

Post-session measures. Several measures were collected periodically for up to 4 days after completion of each experimental session. Data collection was conducted by nursing personnel on the residential unit, and all questionnaires were computerized. Subjects responded on the same Visual Analog Scale and Adjective Rating Scale described above. Nursing personnel rated subjects for opiate

effects with the same Adjective Rating Scale and obtained pupil photographs. Each of these measures was collected at 9, 12, 36, 48, 60, 72 and 96 hr after drug administration.

Pharmacokinetic Analysis of LAAM in Plasma

Blood samples were collected 30 min before and at 1, 5, 15, 30 and 45 min, and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 9, 12, 36, 48, 60, 72 and 96 hr after drug administration. Approximately 8 ml of blood was drawn through an intravenous catheter in the antecubital vein on the arm opposite the one where the intravenous infusion was administered. Samples were drawn into a heparinized vacutainer and immediately centrifuged at 3000 rpm for 10 min. The plasma was removed and frozen at −30°C until the time of assay. Samples were assayed by the Center for Human Toxicology, Salt Lake City, UT for concentrations of LAAM, nor-LAAM and dinor-LAAM by a gas chromatography/positive ion chemical ionization-mass spectrometric method that has been described previously (Moody *et al.*, 1995). The lower limit of sensitivity for the assay was <5 ng/ml.

Pharmacokinetic parameters of LAAM, nor-LAAM and dinor-LAAM were obtained by use of model-independent methods (Gibaldi and Perrier, 1982). The plasma AUC was calculated by the trapezoidal rule from 0 to 96 hr after dose administration [AUC (0–96)]. The elimination rate constant (λ_z) was estimated by linear regression of the last 3 to 4 plasma concentration data points of the terminal postdistribution phase. The terminal half-life ($T_{1/2}$) was estimated from $0.693/\lambda_z$. The AUC (∞) was calculated as follows: AUC (∞) = AUC (0–96) + C_t/λ_z, in which C_t represents the last point plasma concentration. The apparent total body clearance (CL) of LAAM was calculated according to the formula: CL = dose/AUC∞.

The apparent oral total body clearances of nor-LAAM and dinor-LAAM were calculated as the product of CL/F and F where F is the fraction of the dose absorbed. Mean residence time was calculated as the ratio of the area under the first moment curve extrapolated to infinity to AUC(∞). C_{max} and T_{max} are the peak plasma concentrations and time-to-peak concentrations observed rather than calculated, respectively. The observed absolute bioavailability of LAAM (F_{obs}) was determined according to the relationship: $F_{obs} = (AUC_{oral}/AUC_{i.v.}) \times (dose_{i.v.}/dose_{oral})$.

Data Analysis

The time-course data served as the primary analyses for all dependent measures except for the plasma data. Time-course data were analyzed by two-factor ANOVA (drug condition × time). For all measures collected during the experimental sessions, time course was analyzed for the 8 hr after drug administration. Physiological data collected on-line during the session (*i.e.,* heart rate, blood pressure, skin temperature and oxygen saturation) initially were summarized into 15-min averages for each subject (one interval at baseline and 32 intervals after drug administration), thus corresponding with the schedule of data collection for respiratory rate, pupil diameter and questionnaires. Measures that were collected during the experimental session and on the residential unit were analyzed as time course up to 96 hr after drug administration (including visual analogs, subject- and observer-rated adjectives, pupil diameter and plasma).

Further analyses were conducted with AUC and peak minimum and maximum scores where appropriate by one-factor ANOVA. Results were generally consistent with the outcome for main effects of LAAM condition from the time-course analysis, and therefore, are reported only when the results between the analyses differ. To determine the time required for the peak response to occur, the time at which the peak difference score from baseline (either an increase or decrease) was determined for each individual subject and these scores were then averaged across the group. "Time-to-peak" data were generated from the 96-hr time course when available and from the 8-hr time course for those measures collected only during the experimental session. These data were analyzed by one-factor ANOVA. For all analyses, significant main and interaction effects were evaluated further by use of post hoc tests, including ANOVA and/or Tukey's tests where appropriate. All repeated measures data were adjusted for sphericity by Huynh-Feldt corrections. Statistical significance was indicated when $P \leq .05$.

Results

Pharmacodynamic Effects of LAAM

Onset of pharmacological action. Data shown in figure 1 represent the early portion of the time-action curve (*i.e.,* the first 3 hr after drug administration) and are used to illustrate the initial response to oral and intravenous LAAM administration. Scores on two representative visual analog measures, "any drug effect" and "liking," are shown (upper and middle panels). The magnitude of effects on these measures was dose-related for LAAM regardless of whether the drug was administered orally or intravenously. Statistical comparisons (see table 1) revealed that for the measure "any drug effect," scores after LAAM given intravenously were elevated significantly above baseline within 5 min after administra-

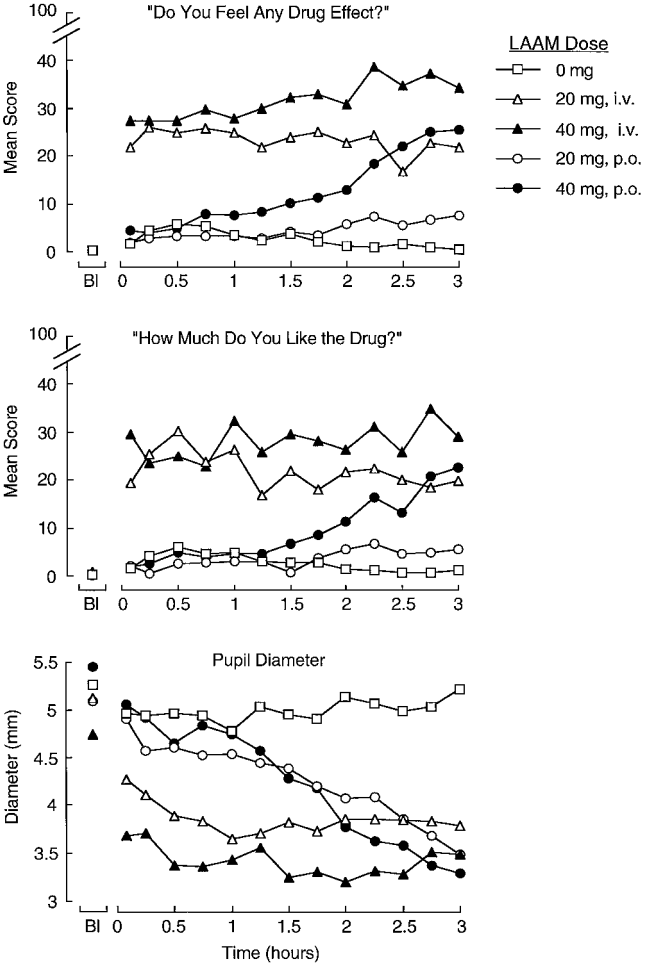

Fig. 1. These three panels illustrate the mean values obtained from six subjects on the subject-rated visual analog measures "Do you feel any drug effect?" (top panel), "How much do you like the drug?" (middle panel) and from pupil photographs (bottom panel). Data are shown for only the first 3 hr of the experimental session to illustrate the latency to onset of drug action. Values shown for baseline (Bl) were collected 30 min before drug administration. Data are shown for the five randomized LAAM dose conditions administered under double-blind and double-dummy conditions. The statistical outcomes are reported in table 1.

tion of both the 20- and 40-mg doses ($P < .05$; Tukey's test). In contrast, the effects of LAAM given orally appeared more slowly. Oral LAAM at 40 mg produced significant score elevations by 2.5 to 3.0 hr for these measures; whereas the low dose of oral LAAM (20 mg) failed to produce significant score elevations on any of the visual analog measures throughout the full 96-hr time course. The profile of LAAM effects shown in figure 1 is similar to that obtained for the visual analog measures of "high" and "good effects" (table 1). LAAM did not significantly alter ratings of "bad effects," "feel sick" or "desire for opiates."

All active doses of LAAM significantly decreased pupil diameter as assessed during the 96-hr time course (table 1). Data are shown in figure 1 (lower panel) for the pupillary response to intravenous and oral LAAM during the first 3 hr after drug administration. As shown, the miotic effects of intravenous LAAM were apparent within 5 min after both 20 and 40 mg; the maximum effect for these intravenous doses occurred at approximately 1 to 1.5 hr after administration. In contrast, both oral doses of LAAM produced significant miosis but this developed during a more protracted time. Significant miosis, relative to baseline, was not observed after oral administration until 2.5 and 1.5 hr after dosing with the 20- and 40-mg p.o. doses, respectively (Tukey's test; $P < .05$). The maximum pupillary effects for oral LAAM were not achieved until 9 to 12 hr postadministration, as described in the next section.

Profile, magnitude and duration of action. *Subjective and observer-rated measures.* The subjective effects of LAAM generally were dose related regardless of the route of administration; however, in most cases the 20-mg dose of oral LAAM did not produce significant elevations on subjective indices of opioid effects. As described above, both intravenous doses (20 and 40 mg) and 40 mg of oral LAAM significantly increased visual analog ratings of positive drug effects including "any drug effect," "liking," "high" and "good effects." Data collected during the full 96-hr time course for the measure "How high are you?" are shown in figure 2 (upper panel); these data generally are illustrative of the time-action and dose-response profiles obtained for LAAM. As can be seen, the overall magnitude of the subjective response to intravenous LAAM was greater when compared with responses after administration of the identical oral dose of LAAM during the early portion of the time-action curve. Thus, the response to 40 mg intravenous LAAM was statistically greater than the response to 40 mg oral LAAM for approximately the first 2 hr after drug administration (Tukey's test; $P < .05$); the same pattern was found for the 20-mg intravenous and oral doses and these differences were apparent for up to approximately 9 hr. During the latter portion of the time course when the effects of LAAM were beginning to decline (*i.e.*, after approximately 9 hr), the magnitude of LAAM effects were generally comparable across the two routes. Despite the noticeable differences in the magnitude of drug effects during the early portion of the time-action curves produced by intravenous and oral LAAM, comparison of the AUC values which include both duration and magnitude of effects did not reveal any statistically significant differences between equal doses of LAAM given orally *versus* intravenously.

The time required to reach peak effect on these visual analog measures also differed between the intravenous and oral routes. For each of the measures that were significantly altered by LAAM (see table 1), the time to reach peak response was faster after administration of intravenous LAAM than oral LAAM; this was true regardless of the test dose. For example, average time required to achieve the peak

TABLE 1

Statistical results for the time-course analyses of LAAM

Values shown are P values; those in italics indicate trend values where $P < .10$ but $> .05$. Measures for which no significant main effects of LAAM or LAAM dose by time interactions were obtained are not included in this table. Significance was determined when $P \leq .05$. Arrows indicate the direction of effect relative to placebo.

	LAAM Condition	Dose × Time	Direction of Change
Visual analogs[a]	*dF(4,20)*	*dF(168,840)*	
High	0.016	0.000	↑
Drug effect	0.006	0.000	↑
Good effects	0.000	0.001	↑
Drug liking	0.001	0.000	↑
Adjective rating scales[b]	*dF(4,20)*	*dF(64,320)*	
Subject-rated			
Nodding	0.000	0.031	↑
Skin itchy	0.099		↑
Heavy/sluggish feeling	*0.077*		↑
Coasting	0.023		↑
Agonist scale	*0.054*		↑
Fraser scale	0.002	*0.058*	↑
Observer-rated			
Nodding	0.002	0.000	↑
Skin itchy	0.001	0.001	↑
Heavy/sluggish feeling	0.042	0.000	↑
Dry mouth	0.016	0.000	↑
Good mood	0.035		↑
Sleepy	0.015	0.002	↑
Physiological effects			
	dF(4,20)	*dF(168,840)*	
Pupil diameter[a]	0.000	0.000	↓
	dF(4,20)	*dF(128,640)*	
Oxygen saturation[b]	*0.055*	0.005	↓
Heart rate[b]	*0.055*		↓
Systolic blood pressure[b]		0.018	↓
Skin temperature[b]	0.044	0.017	↑

[a] 96-hr time-course analysis.
[b] 8-hr time-course analysis.

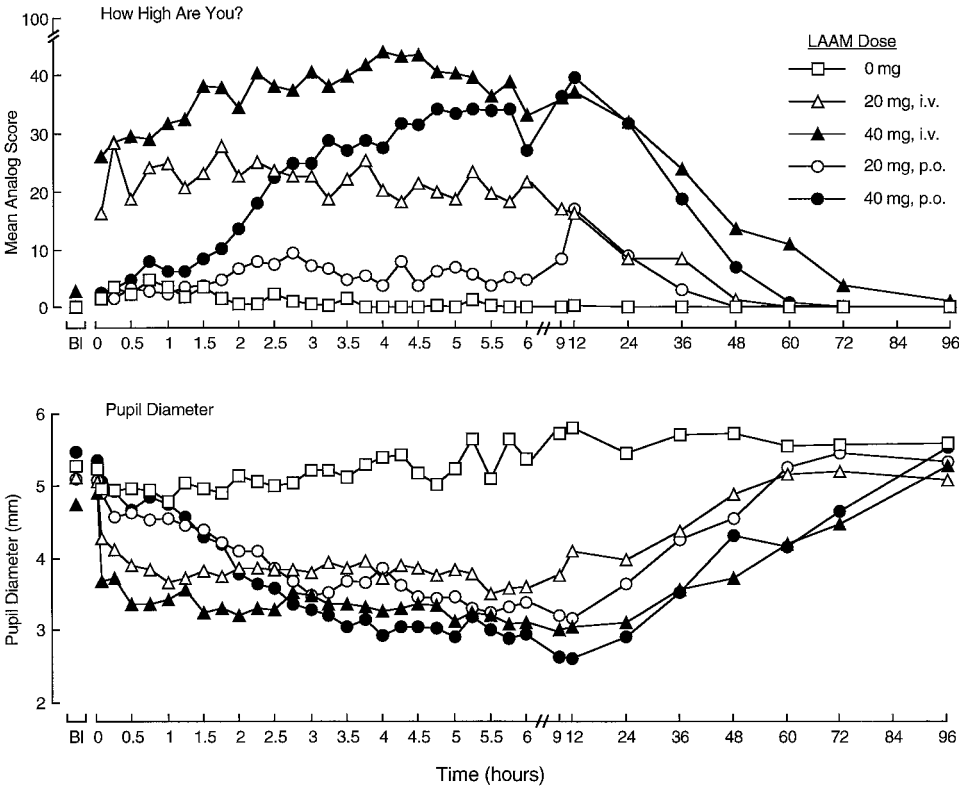

Fig. 2. Mean data (n = 6) are shown for the full 96-hr time course after administration of LAAM on the visual analog measure "How high are you?" (upper panel) and for pupil diameter (lower panel). Values shown for baseline (Bl) were collected 30 min before drug administration. The hatch marks along the x-axis indicate only a change in the time between tick marks (*i.e.*, from 30 min to 12 hr per segment). The results of the statistical analyses for these data are reported in table 1 and described in the text.

response for the measure "Do you feel any drug effect?" was 3.4 and 4.6 hr after intravenous administration of 20 and 40 mg LAAM. In contrast, the peak response after these same doses of oral LAAM was not achieved until 8.3 and 10 hr for the 20- and 40-mg doses, respectively. The results for the time-to-peak analysis for other measures (*i.e.*, "high," "liking for the drug") were concordant with the results reported here for the measure of magnitude of drug effect.

LAAM administered orally and intravenously produced subjective responses of long duration. *Post hoc* analyses of visual analog data collected for 96 hr after acute dosing revealed that scores on measures including "high," "drug effect," and "liking" were elevated significantly in comparison with placebo for up to 12 hr and 36 hr after intravenous LAAM at 20 and 40 mg, respectively (Tukey's test, $P < .05$). As described previously, the low dose of oral LAAM (20 mg) failed to produce significant increases on these measures at any time; however, for the 40-mg oral dose of LAAM scores remained significantly elevated for up to 24 hr after dosing compared with the placebo control condition (Tukey's test; $P < .05$).

Administration of LAAM significantly increased subjective ratings on only a few items from the 38-item adjective checklist (table 1). Ratings of nodding and coasting were increased significantly ($P \leq .05$), whereas marginal increases were observed on ratings of itchy skin and heavy/sluggish feeling ($P < .10$). Each of these items are descriptive of prototypic opioid agonist effects. Scores on the composite Fraser scale, also sensitive to opioid agonist effects, were elevated significantly by all active doses of LAAM in comparison with placebo (Tukey's test, $P < .05$). The results for the observer-rated adjective checklists were remarkably similar to those obtained from the subjects (table 1). Observers rated significant increases after administration of LAAM in comparison with placebo on the following measures: nodding; skin itchy; heavy/sluggish feeling; dry mouth; good mood; and sleepy. Observers rated significant increases on at least one of these prototypic opioid agonist items after administration of all active doses of LAAM; however, these effects were more pronounced for the high dose (40 mg) than the low dose (20 mg) regardless of whether the drug was administered intravenously or orally. The observer ratings were also sensitive to the difference in latency to onset of drug effect for the two routes of administration. For example, ratings of "itchy skin" were elevated significantly within 1.5 hr of administration of 40 mg of intravenous LAAM in contrast to 3.5 hr for the same dose given orally (Tukey's test; $P \leq .05$).

LAAM did not significantly alter any of the ARCI subscales during the 8-hr experimental session. There was a nonsignificant trend ($P = .061$) for scores on the PCAG-Sedation Scale to increase during the active dose sessions. There were also significant main effects of time for the PCAG and the BENZ scales ($F[16,80] = 2.94$ and 2.36, respectively; $P < .05$), whereby the PCAG scores increased and the BENZ scores decreased as a function of time in session.

Physiological measures. Pupillary response proved to be the most sensitive physiological index of LAAM action under these dosing conditions, and therefore, these data are used to describe the time-action and dose-response effects of LAAM. Data for pupil diameter are shown for the full 96-hr time course in the lower panel of figure 2. As already described, intravenous LAAM produced miosis more rapidly than oral LAAM. For intravenous LAAM, the degree of pupil constriction was dose-related; the low dose (20 mg) produced less constriction than the high dose (40 mg). The duration of action was also related to dose, with significant miosis persisting for 36 hr after 20 mg but 72 hr after 40 mg (Tukey's test; $P \leq .05$). In contrast to the failure of oral LAAM at 20

mg to produce any appreciable subjective effects, this dose produced significant pupillary constriction, relative to base line, within 2.5 hr, which persisted for 48 hr after dosing (Tukey's test; $P \leq .05$). LAAM, 40 mg given orally, produced significant pupillary constriction from 2 to 60 hr after dosing. Despite the observable differences for rate of onset and decline of miosis, analysis of the AUC values for pupil diameter did not reveal significant *post hoc* differences between the two routes of administration or between LAAM doses.

LAAM produced few other pronounced physiological effects when administered across this dose range. LAAM did not produce large or clinically significant reductions in oxygen saturation. The main effect of LAAM dose on oxygen saturation failed to reach significance ($P = .055$), whereas there was a significant LAAM dose × time interaction on oxygen saturation (table 1). However, the maximum observed decline in oxygen saturation was less than 2% after any active LAAM dose. No significant effects of LAAM were observed on respiratory rate.

Analysis of the 8-hr time course revealed that LAAM did not significantly alter heart rate or systolic or diastolic blood pressure. Analysis of the peak responses (minimum or maximum) confirmed the findings for physiological measures with one exception. Compared with placebo, heart rate was decreased significantly by active LAAM doses when assessing the maximum decrease for the session ($F(4, 20) = 5.01$; $P = .009$), with the greatest decrease (7 bpm) occurring after administration of 40 mg intravenous LAAM (Tukey's test; $P < .05$). LAAM produced a main effect on skin temperature as well as a dose × time interaction (table 1). These resulted from the tendency for active LAAM doses to increase skin temperature modestly in contrast to the decline in skin temperature observed during the course of the 8-hr session after placebo administration.

Pharmacokinetic Profile

Plasma concentrations of LAAM and its metabolites, nor-LAAM and dinor-LAAM, were measured throughout the 96-hr time course after dosing. Figure 3 illustrates the concentrations of the parent drug, LAAM, after administration by the oral and intravenous routes at 20 mg (left panel) and 40 mg (right panel). Concentrations of LAAM in plasma increased with dose regardless of route of administration; however, these increases were not dose-proportional. For example, the differences in the AUC values for LAAM when comparing the 20-mg dose with the 40-mg dose were approximately 2.5- and 2.4-fold greater for intravenous and oral administration, respectively (table 2). Moreover, LAAM clearance and half-life are increased at the higher dose for both the oral and intravenous conditions. Together these data suggest a trend toward nonlinear kinetics for LAAM itself, although linearity cannot be assessed accurately with these data because only two active doses were administered. Statistical comparison of LAAM clearance and half-life values for the 20 and 40 mg doses revealed no significant dose-related differences on these parameters ($P > .05$; paired sample two-tailed t tests), although power is limited to detect a difference with the small sample size. The estimated half-life of LAAM was excluded from the analysis for one subject because it was determined to be an outlier according to Dixon's test ($r_{01} = 0.82$; $P < .005$; Dixon, 1951). The estimated half-life for this subject (125 hr) resulted from the plasma values over the latest portion of the time-action curve (*i.e.,* 48–96 hr) showing a relatively flat function with limited decline.

Intravenous administration of LAAM led to significantly higher peak concentrations of LAAM (C_{max}) than oral administration for both the 20- and 40-mg doses; the C_{max} values were approximately 5- and 12-fold higher for intravenous LAAM at 20 mg and 40 mg, respectively (table 2). LAAM was distributed rapidly after intravenous administration as evidenced by the rapid peak and decline in the first 5 min after infusion. The time frame in which LAAM could be detected in plasma was dose related; LAAM was detectable in plasma for 36 hr and 72 hr after administration of the 20- and 40-mg doses, respectively. Bioavailability estimates generated from comparison of the intravenous and oral dose conditions suggest that the parent drug LAAM has an oral bioavailability of approximately 47 to 48% (table 2).

The concentrations of the two metabolites, nor-LAAM (upper panel) and dinor-LAAM (lower panel), are shown in figure 4. These data are shown on a log scale ranging to 100 ng/ml in contrast to the scale for LAAM concentrations

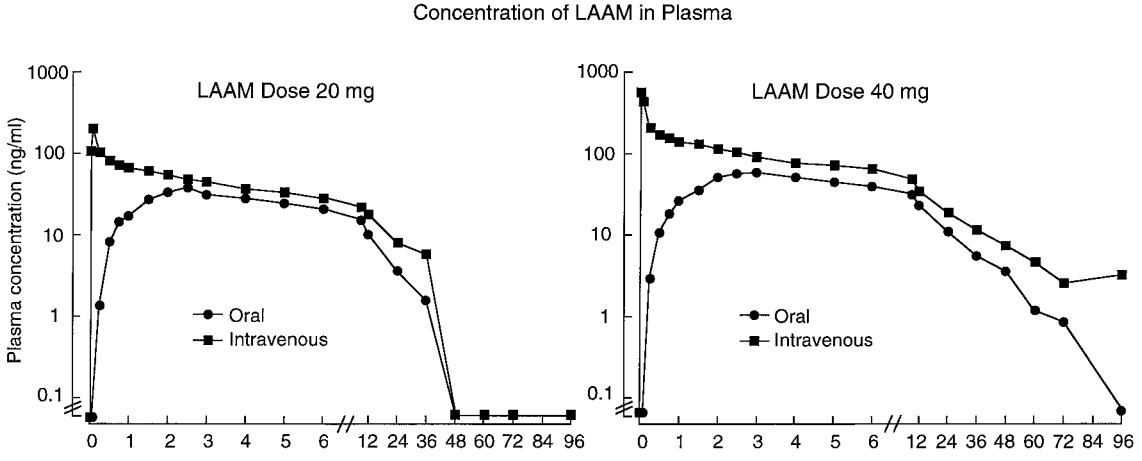

Fig. 3. The mean ($n = 6$) concentrations of the parent drug LAAM found in plasma are shown for all active dosing conditions. Concentrations of LAAM after administration of 20 mg (left panel) and 40 mg (right panel) are shown for oral (closed circles) and intravenous (closed squares) administration. Data are shown on a logarithmic/linear scale. Hatch marks along the x-axis indicate only a change in the time between tick marks (*i.e.*, from 1 to 12 hr per segment).

TABLE 2
Pharmacokinetic parameters derived from a noncompartmental modeling method for LAAM and its two principal metabolites in plasma after intravenous and oral administration

	20 mg i.v.[a]	40 mg i.v.	20 mg p.o.	40 mg p.o.
LAAM				
C_{max} (ng/ml)	212 (±32)	756 (±229)	39 (±7)	63 (±8)
$T_{1/2}$ (hr)	14.3 (±1.7)	20.9 (±3.6)[b]	7.9 (±1.2)	18.5 (±4.9)
AUC (∞) (ng/ml · hr)	793 (±53)	2028 (±275)	393 (±85)	944 (±128)
T_{max} (hr)	0.06 (±0.01)	0.06 (±0.01)	2.5 (±0.4)	2.6 (±0.2)
CL (ml/hr/kg)	352 (±25)	295 (±35)	357 (±25)	296 (±35)
MRT (∞)[c] (hr)	16.4 (±1.9)	36.5 (±15.6)	12.2 (±1.8)	23.8 (±5.0)
F_{obs}	–	–	0.48 (±0.09)	0.47 (±0.05)
nor-LAAM				
C_{max} (ng/ml)	13 (±1)	26 (±2)	26 (±3)	44 (±4)
$T_{1/2}$ (hr)	30.3 (±5.2)	37.9 (±5.4)	33.6 (±4.2)	23.9 (±3.2)
AUC (∞) (ng/ml · hr)	684 (±120)	1666 (±275)	994 (±192)	1516 (±200)
T_{max} (hr)	4.5 (±1.7)	8.0 (±3.4)	3.1 (±0.5)	3.9 (±0.7)
dinor-LAAM				
C_{max} (ng/ml)	9 (±0)	15 (±1)	12 (±1)	19 (±1)
$T_{1/2}$ (hr)	88.9 (±39.9)	80.5 (±14.7)	75.6 (±15.4)	65.8 (±10.1)
AUC (∞) (ng/ml · hr)	1292 (±342)	2344 (±309)	1516 (±295)	2313 (±363)
T_{max} (hr)	40.8 (±7.4)	48.0 (±6.2)	17.9 (±7.3)	31.0 (±9.6)

[a] Data are reported as the mean value (n = 6) ± 1 S.E.M.
[b] Data for one outlier subject were excluded as described in the text.
[c] MRT, mean residence time.

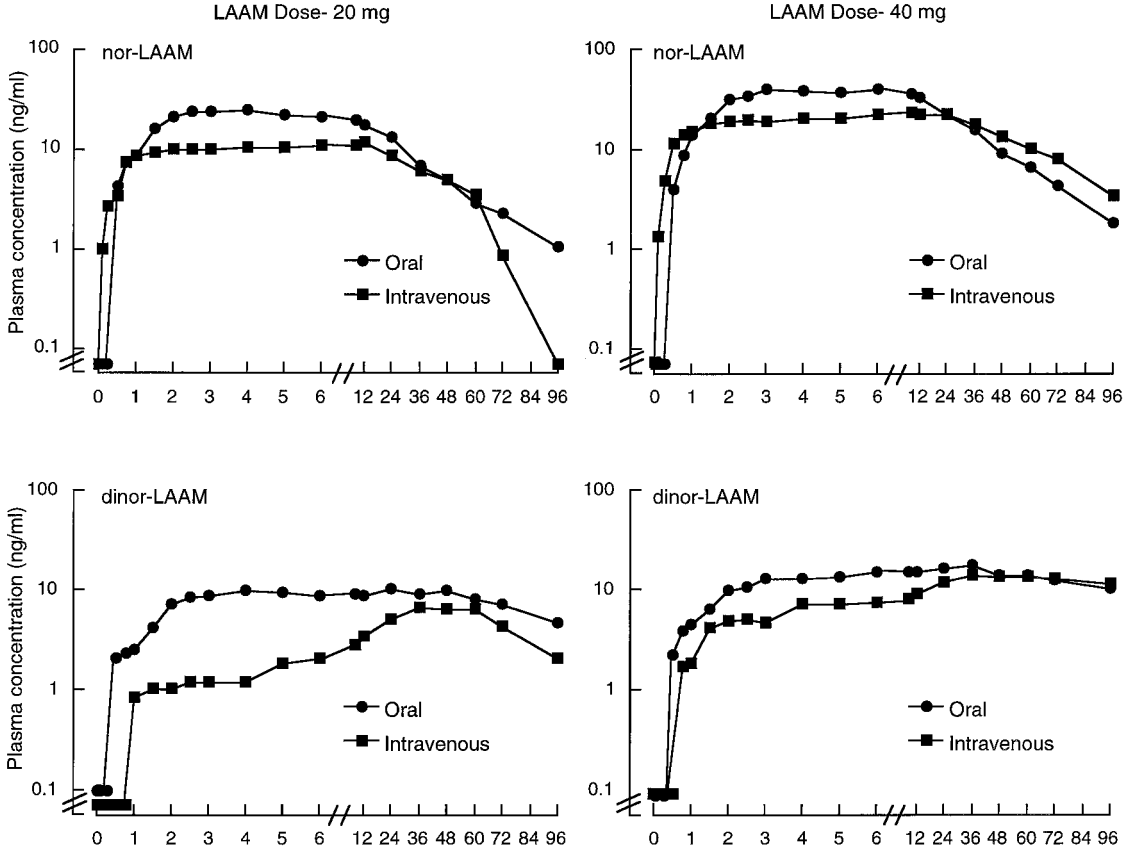

Fig. 4. The mean (n = 6) concentrations of nor-LAAM (upper panels) and dinor-LAAM (lower panels) are shown for all active dosing conditions. Data after administration of 20 mg (left panels) and 40 mg (right panels) are shown for oral (closed circles) and intravenous (closed squares) administration. The hatch marks along the x-axis indicate only a change in the time between tick marks (*i.e.*, from 30 min to 12 hr per segment).

shown in figure 3, which ranges up to 1000 ng/ml. The sequential nature of the metabolic path (*i.e.*, LAAM→ nor-LAAM → dinor-LAAM) is evidenced by 1) the time-ordered appearance of LAAM, nor-LAAM and then dinor-LAAM, respectively, in plasma under all dosing conditions; 2) the time-ordered T_{max} values describing the time required to reach peak plasma concentration (table 2); and 3) the sequential disappearance from plasma of LAAM, nor-LAAM and dinor-LAAM (see figs. 3 and 4). Administration of LAAM by the oral route reliably produced higher concentrations of nor-LAAM and dinor-LAAM than intravenous administration for both LAAM doses from approximately 2 to 24 hr after drug administration (see fig. 4). However, AUC values differed across routes only for the 20-mg dose of LAAM and were

similar after administration of the 40-mg dose (see table 2). Both metabolites were present in plasma at 96 hr after a single intravenous or oral dose of 40 mg; their long duration of action is also apparent from the calculated $T_{1/2}$ values which ranged from 24 to 38 hr for nor-LAAM and from 66 to 90 hr for dinor-LAAM (see table 2). Residual dinor-LAAM was detected 1 week after LAAM administration on three single occasions as illustrated by the modest baseline elevations for dinor-LAAM shown in figure 4.

Side Effects

Although there was no significant main effect of LAAM condition on the visual analog measure "Does the drug make you feel sick?," there was a significant effect of time (F[41,205] = 2.95; P = .021). *Post hoc* analyses revealed that the 40-mg dose of LAAM given both orally and intravenously significantly increased ratings of "sick" compared with placebo during the latter portion of the time course (*i.e.*, between 12 and 24 hr after dosing). Moreover, review of the medical charts revealed that vomiting occurred in response to LAAM administration in at least half of the subjects after administration of LAAM at 20 and 40 mg p.o. and 40 mg i.v. at some point during the 96 hr after acute dosing.

Discussion

This study demonstrates that intravenous administration of LAAM produces pronounced subjective and physiological effects in humans that appear almost immediately after infusion and more rapidly than those produced by LAAM given orally. The pharmacokinetic analyses reveal that these effects appear at a time when LAAM, but not its active metabolites nor-LAAM and dinor-LAAM, are detected in plasma. These data suggest that the parent drug is primarily responsible for producing these immediate effects, and thus, LAAM is pharmacologically active in humans when administered parenterally and should not be characterized as merely a prodrug. These findings are in contrast to current beliefs that arose primarily from two previous clinical studies that reported an unusually slow onset for the effects of intravenous and subcutaneous LAAM in comparison with oral LAAM (Fraser and Isbell, 1952; Fraser *et al.*, 1954), but are in agreement with several preclinical studies that have reported a shorter latency of onset for parenteral LAAM effects (*e.g.,* Henderson, 1976a, 1976c; Archer, 1976).

Consistent with the classification of LAAM as a pure *mu* agonist, the profile of effects produced by LAAM in the present study was *mu* agonist-like. LAAM produced significant pupillary constriction, and elevated subject-rated and observer-rated scores on an array of global measures of euphoric effects (*e.g.*, "high" and "liking" for the drug) as well as prototypic opioid agonist effects (*e.g.*, itchy skin and nodding). The magnitude of these effects was generally dose dependent regardless of the route of administration. The response to intravenous LAAM occurred within 5 min of infusion in all subjects; significant miosis and elevations of subjective ratings of drug effect and euphoric effects were immediately apparent, whereas the peak effects were substantially delayed and occurred within 4 to 5 hr after infusion. In contrast, the effects of LAAM given orally appeared within 1 to 2 hr after dosing and continued to rise, peaking between 8 and 12 hr after dosing, depending on the measure (see fig. 2). This time-action profile for oral LAAM is consistent with previous studies that have characterized the response to acute doses of oral LAAM in dogs (Henderson, 1976c), monkeys (Henderson, 1976a, b) and humans (Fraser and Isbell, 1952; Irwin *et al.*, 1976; see also Sollod and Goldstein, 1976). Although the onset of intravenous LAAM effects was faster than that of oral LAAM, no statistical between-route pharmacodynamic differences were found for the calculated peak responses and AUC values obtained for a given dose (*e.g.*, 20-mg oral compared with 20-mg intravenous), which suggests no overall differences in the magnitude of the pharmacodynamic effects between the two routes of administration.

Our findings on the immediate response to intravenous LAAM are in direct contrast to those of the early parametric study published by Fraser and Isbell (1952). Although it is impossible to reconcile the results of these studies retrospectively, it is plausible that specific methodological differences contributed to these contradictory findings, including the 1) dose ranges, 2) dependent measures and 3) subject populations. In the early study, intravenous LAAM was evaluated across a range of test doses (*i.e.*, 10–30 mg) that was somewhat lower than tested in the present study (*i.e.*, 20–40 mg). Given a relative potency estimate ratio of 1:1.2 of methadone/LAAM, the highest test doses in these studies (30 and 40 mg) are approximately equivalent to oral doses of 25 and 33 mg of methadone, respectively. These doses may, in fact, be fairly low when one considers that participants in both studies were experienced opioid users with some level of opioid tolerance. This suggestion is supported by findings in the present study that oral LAAM at 20 mg failed to produce any significant subjective effects and oral and i.v. LAAM at 40 mg failed to alter some indices typically sensitive to opioids, including the ARCI, adjective composite scales and respiration (*e.g.,* Jasinski and Preston, 1986; Walsh *et al.*, 1994; Zacny *et al.*, 1994). The earlier study relied solely on clinical observation techniques rather than the controlled physiological and self-report measures used in the present study. Finally, although limited detail is provided regarding the drug histories of participants in the Fraser and Isbell study, it is stated that patients had a recent history of morphine addiction but were withdrawn at the time of the study, a standard practice in early opioid studies at the Lexington Addiction Research Center. It is possible, therefore, that their study population may have been more tolerant than our nondependent sporadic opioid abusers. Thus, it is plausible that administration of relatively low LAAM doses to opioid-tolerant individuals coupled with sole reliance on observational measures may have occluded the detection of drug effects in this earlier study. Fraser and Isbell reported that intravenous LAAM produced measurable effects by 4 to 6 hr after drug administration; this time frame corresponds with the time when the peak subjective responses to intravenous LAAM were observed in the present study.

Another difference between the present study and the earlier study is that the subjects in the present study were all African American, whereas the subjects in the Lexington study were all Caucasian. This potentially could be important if there are significant racial differences in sensitivity to or metabolism of LAAM. It is well known that certain enzyme systems involved in drug metabolism, such as P450 2D6, exhibit genetic polymorphisms that can lead to significant

interindividual metabolic differences. LAAM is metabolized primarily through N-demethylation to its active metabolites (*e.g.*, Kaiko and Inturrisi, 1975; Chiang *et al.*, 1995), and recent data from *in vitro* human liver metabolic studies suggest that cytochrome P450 3A4 is the enzyme primarily involved in the production of nor-LAAM and dinor-LAAM (Moody *et al.*, 1997). Although there is no current evidence supporting the existence of polymorphic forms of P450 3A4 (Wilkinson, 1996), the possibility of genetic variants cannot be ruled out and neither can the participation of other P450 enzymes in the metabolism of LAAM. Thus, although existing evidence does not support the argument that significant metabolic differences exist or that other critical pharmacokinetic or neurochemical factors vary across these two racial groups, the potential influence of such differences cannot be excluded as factors contributing to the differential outcome of these two studies.

Consistent with previous studies, these data indicate that LAAM is extraordinarily long acting and produces measurable pharmacodynamic effects for 48 to 60 hr after a single dose. The duration of action was dose related, with larger doses producing more sustained effects than lower doses, and was equivalent after intravenous and oral administration. The calculated half-life estimates ranged from 14 to 37 hr for LAAM, and 24 to 38 hr for nor-LAAM with some variability caused by individual differences, as well as dose and route differences (see table 2). These values are generally within the range of previous estimates (Billings *et al.*, 1973; Chiang *et al.*, 1995). The estimated half-life for dinor-LAAM ranged from 66 to 89 hr across conditions; although these values are also similar to previous reports (Chiang *et al.*, 1995), the sampling period was equivalent to roughly only one half-life and the calculations required more extrapolation than desirable for an accurate estimate.

Previous studies have attempted to correlate the time-action profile of LAAM with the presence of LAAM and its metabolites in plasma to identify the compound that best accounts for the pharmacodynamic effects. The present data suggest that all three drugs are active and contribute to the pharmacological activity of LAAM. During the earliest portion of the time-action curve for intravenous LAAM, it is evident that the parent drug is active and producing significant subjective and physiological effects. Pronounced pharmacodynamic effects were observed within 5 min of infusion and LAAM was detected in all subjects during this same period. In contrast, nor-LAAM was detected in only one subject during this early portion of the time curve and was not detected in the other subjects until approximately 45 min postinjection. For all dynamic measures, the effects continued to rise after concentrations of the parent drug had already begun to decline, and concentrations of nor-LAAM and dinor-LAAM were still rising. It is important to note that nor-LAAM has been characterized in preclinical and clinical studies as being substantially more potent than both LAAM and dinor-LAAM (Lukas *et al.*, 1980; Perez-Reyes, 1985; Nickander *et al.*, 1974; Smits, 1974). After all active LAAM doses, dinor-LAAM was still present in plasma at 96 hr after drug administration and showed little sign of decline, yet no residual drug effects were detected at this time under any condition, which suggests the possibility of acute tolerance. Thus, comparison of the time to reach peak effect for miosis and subjective measures (*e.g.*, ratings of "high" or "drug effect") with peak plasma concentrations of drug (see table 2) suggests that the time course for concentrations of nor-LAAM corresponds most closely with the dynamic effects of the drug and this is consistent with other reports (Henderson, 1976a; Henderson *et al.*, 1977c; Perez-Reyes, 1985). The pharmacodynamic effects of LAAM produced by a given dose (*e.g.*, 40 mg) were generally equivalent in magnitude across the time-action curve (*i.e.*, AUC values) regardless of the route of administration; this is surprising in light of the finding that much higher concentrations of the parent drug, LAAM, were achieved by intravenous administration whereas greater nor-LAAM concentrations were achieved by oral administration.

The pharmacokinetic profile of LAAM observed in the present study is complex but consistent with previous reports collected from laboratory animals and humans. After intravenous administration, there was an immediate rise in LAAM concentrations in plasma that peaked between 1 and 5 min after infusion and fell rapidly (*e.g.*, 0–550 ng/ml during 5 min declining to 200 ng/ml at 10 min after 40 mg). This sharp decline suggests that the drug is distributed rapidly to other compartments where it may remain sequestered for some duration given its highly lipophilic character. This rapid peak and distribution is similar to the pharmacokinetic profile of intravenous LAAM when given to both monkeys (Misra and Mule, 1975) and rats (Henderson *et al.*, 1977a). In contrast to i.v. administration, peak concentrations of LAAM were not achieved until 2.5 hr after oral administration of the drug. This time course is also consistent with preclinical and clinical pharmacokinetic studies of oral LAAM dosing (Billings *et al.*, 1974; Henderson *et al.*, 1977b, c; Kaiko and Inturrisi, 1975; Chiang *et al.*, 1995). These present data suggest that the kinetic properties of LAAM may be nonlinear; AUC values increased in a greater than dose-proportional fashion and there was an accompanying trend for clearance and half-life to increase with increasing dose. Although these differences did not achieve statistical significance, a fuller dose-effect evaluation will be required to characterize and model the pharmacokinetic profile of LAAM.

The maximum plasma concentration (*i.e.,* C_{max}) of LAAM achieved after intravenous administration was roughly 5.5- and 12-fold greater than for oral LAAM at 20 and 40 mg, respectively. This is consistent with another study that evaluated the pharmacokinetics of LAAM in monkeys and found lower peak levels of free parent drug after oral *versus* parenteral (*i.e.*, subcutaneous) LAAM (Misra and Mule, 1975). Despite the large differences observed in initial circulating concentrations of parent compound in this study, subsequent peak and AUC concentrations of nor-LAAM and dinor-LAAM were roughly equivalent between the routes or even higher after oral compared with intravenous dosing. This is not necessarily unexpected because the oral dose, but not the intravenous dose, can be subjected to first-pass metabolism potentially leading to greater biotransformation to the active metabolites. A large first-pass effect for oral LAAM is supported by the finding in the present study that the bioavailability estimates for oral LAAM were less than 50%. Although no previous controlled comparisons of intravenous and oral LAAM in humans were found in the literature, a preclinical study conducted in rats reported similar results estimating the oral bioavailability of LAAM to be approximately 60% (Henderson *et al.*, 1977a). The

pharmacokinetic profile for LAAM under these acute dose conditions is likely to be dissimilar to that observed during chronic LAAM administration. Because the active metabolites tend to accumulate with repeated dosing (Billings *et al.*, 1974), it would be expected that the parent/metabolite ratio would decrease under chronic dosing conditions.

In summary, the present results indicate that LAAM administered intravenously produces opioid agonist effects that appear immediately after infusion; this finding is in contrast to previous clinical studies that reported a delayed onset of action for parenteral LAAM. The immediate onset of action after intravenous LAAM is primarily attributable to the pharmacological activity of the parent drug, rather than the demethylated metabolites, which indicates that LAAM is not merely an inactive prodrug. LAAM given orally and intravenously was equieffective in producing a constellation of prototypic opioid agonist effects of long duration, although the relative contributions of the parent drug and metabolites to these pharmacodynamic actions varied across the two routes of administration. These data suggest that LAAM possesses abuse potential; the gradual onset of effects after oral administration is likely to minimize the risk of abuse by the oral route. However, the slow onset of effects produced by the metabolites after oral dosing justifies the labeling recommendations to warn patients that toxicity may result if other drugs are taken after LAAM administration. The rapid onset of effects after intravenous LAAM indicates that the risk for abuse and diversion to the parenteral route may be substantially greater than previously believed. Because the commercially available product is formulated as a clear concentrated aqueous solution that could be injected easily, these data suggest that care should be exercised in the preparation of clinical doses to dilute the concentrate in a vehicle with physical properties that will deter parenteral use.

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