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The Effects of Acetylmethadol on Motor Activity and Schedule-Controlled Responding

W. T. MCGIVNEY[1] AND D. E. MCMILLAN[1]

Departments of Pharmacology
University of North Carolina, School of Medicine, Chapel Hill, NC 27514 and
University of Arkansas Medical Sciences Campus, Little Rock, AR 72201

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MCGIVNEY, W. T. AND D. E. MCMILLAN. *The effects of acetylmethadol on motor activity and schedule-controlled responding*. PHARMAC. BIOCHEM. BEHAV. **10**(2) 261–265, 1979.—The effects of levo-alpha-acetylmethadol (LAAM) on locomotor activity and operant behavior were examined in rats. LAAM increased locomotor activity when given intraperitoneally (IP) at doses of 1 mg/kg and 3 mg/kg, but 10 mg/kg produced a slight decrease in motor activity over the 10-hour period. The largest increases and decreases in locomotor activity occurred 6–8 hours after administration of the drug. Other rats were trained to lever press for food pellets under a fixed-interval 90-second, fixed-ratio 10-response multiple schedule. LAAM only decreased rates of responding under the multiple schedule. Marked decreases in rates of responding under both components of the schedule occurred when LAAM was administered IP either 3 or 6 hours before the session at doses of 3 mg/kg and 10 mg/kg. The rate-decreasing effects of LAAM became greater the longer the interval between administration of the drug and initiation of the session.

Levo-alpha-acetylmethadol Motor activity Schedule-controlled responding Time course Peak effect Duration of action

LEVO-alpha-acetylmethadol (LAAM), a derivative of *d*-methadone, is currently being examined clinically as an alternative to methadone in the maintenance treatment of heroin addicts. LAAM was first synthesized in 1948, and early investigational work focused on its potential analgesic activity [3,17]. In 1952, LAAM's usefulness in preventing the withdrawal symptoms normally associated with the abrupt discontinuation of heroin use in addicts was first recognized [9]. In 1970, attention was refocused on LAAM's possible utility as a long acting substitute for methadone in the maintenance treatment of addicts [16]. The advantages of LAAM in the treatment of opiate addiction are ascribed to its gradual onset of action and its ability to suppress narcotic withdrawal symptoms for up to 72 hours [10,24]. To date, very little attention has been given to the behavioral effects of LAAM in experimental animals. In the present study, the effects of LAAM on locomotor activity and operant behavior were examined in male rats.

Previous behavioral work with narcotics has shown that morphine, at low doses, will produce increases in locomotor activity in rats [1,22] and in mice [26,31]. Also, *l*-methadone has been shown to increase locomotor activity in mice, but *d*-methadone does not [23]. Examination of the effects of morphine and methadone on operant behavior has shown that at low doses both morphine and methadone will increase rates of fixed-interval (FI) responding in many species including rats [29,30] and pigeons [11, 20, 21]. At higher doses, morphine and methadone have been shown to decrease rates of responding under both components of a multiple fixed-interval fixed-ratio (FI FR) schedule of food presentation [11, 20, 21, 32]. Administration of LAAM to Rhesus monkeys at a dose of 2 mg/kg decreased rates of responding under the FR component of a chained schedule of positive reinforcement during a session started 3 hr after LAAM administration and slightly increased the FR response rate if the session was initiated 6 hr after the monkeys received LAAM [8].

In the present study, the effects of LAAM on rates of responding under a multiple FI-90 sec FR-10 schedule were examined with administration of LAAM at 0, 3 and 6 hr prior to initiation of the session. Locomotor activity was also monitored in LAAM treated rats for a 10-hr period to provide an additional measurement of LAAM's onset of action and potency.

METHOD

Animals

For the study of schedule-controlled responding, male Sprague-Dawley rats (n=3) were maintained at 80% (235–275 g) of their free-feeding weights by food presented during the experimental sessions and by post-session supplemental feedings. Male Sprague-Dawley (n=4) rats maintained at a body weight between 200–225 g were used to measure locomotor activity.

[1]Authors' present address is: Department of Pharmacology, University of Arkansas for Medical Sciences, Little Rock, AR 72201.

Apparatus

Rates of lever pressing for food were determined in a sound attenuating Gerbrand's experimental rat chamber. The experimental chamber was 27 cm high × 30 cm wide × 25.5 cm long. The chamber contained two response levers, only one of which was active during the session. A force of 15 g was required to register a response. During reinforcement, a Gerbrand's pellet feeder delivered a 97 mg food pellet (P.H. Noyes Co.). The chamber was illuminated by a 28 V bulb only during the fixed-interval component of the multiple schedule. Responses were recorded on digital counters and on a cumulative response recorder.

Locomotor activity was monitored in two ways. First, a photocell placed in the wall of a circular cage 7.6 cm above floor level transected the midline of the cage (r=14.0 cm, h=33.0 cm) and served to measure the activity of the rats by registering a count every time the beam of light was interrupted. Second, an animal activity chamber (Lafayette Instrument Co., Lafayette, Indiana) with sensitivity settings of gain—9.5 and activity—slow also was used.

Procedure

A multiple fixed-interval 90-sec fixed-ratio 10-response schedule of food presentation (mult FI 90, FR 10) was used to measure rates of lever pressing. During the FI component of the schedule, the chamber was illuminated by the 28 V bulb described above. The first response after the 90-sec interval had elapsed resulted in the presentation of a 97 mg food pellet. Under the FR component of the schedule the light was off and 10 responses were required to produce the pellet. A limited hold of 60 sec applied to both components of the schedule, so that the rat had 60 sec to make the 10 FR responses, or to make a single response after 90 sec had elapsed in the FI component. Schedule components alternated with food delivery or expiration of the limited hold. The length of the session was approximately 55 min and sessions were conducted 6 days a week.

In the study of locomotor activity, activity counts were cumulated hourly for a 10-hr period. Two of the four rats were assigned to the activity chamber and the remaining two to the photocell apparatus. All rats were tested individually.

Measurement of Drug Effects

Responses under the two components of the multiple schedule were sorted into separate digital counters. FI responses were further divided and cumulated during 10 successive time bins of 9 seconds each. Elapsed time for each component of the schedule was recorded and average rates of responding were calculated as % of the control rate of responding. Control values correspond to the rates of responding observed in the daily sessions preceding the second drug day of each week. Quarter-life values were calculated for responding under the FI. The quarter-life is defined as the fraction of the 90-sec interval necessary for the animal to emit 25% of the total responses under this component of the schedule [12]. The data obtained from the ten 9-sec segments were used to show the effect of LAAM on local rates of responding within the FI by expressing the drug data as a percentage of the nondrug rate of responding [18]. Rates of responding under the FI which were less than 0.1 responses per second were not included in the determination of quarter-life values or in the rate-dependency analysis.

The motor activity was computed for each individual animal as percent of the average hourly activity for the control injection and then averaged across the four animals as percent of control.

Drugs

LAAM, kindly supplied by NIDA, was dissolved in distilled water and injected by the intraperitoneal route in ascending and descending doses which were counterbalanced for the animals in each study. The injection volume was 1 ml/kg and injections were spaced at least 96 hours apart.

RESULTS

The effects of LAAM (0.1–10.0 mg/kg) on rates of responding under both components of the multiple schedule, at 0, 3, and 6 hr after drug administration are shown in Fig. 1. Rate-increasing effects were not observed at any dose under either schedule component. Under both schedule components, dose dependent rate-decreasing effects were observed for all three pretreatment times. The magnitude of the rate-decreasing effects of higher doses of LAAM became greater the more extended the interval between administration of the drug and initiation of the session.

LAAM produced a marked disruption of the FI pattern of responding only at the 10 mg/kg dose in the 6 hr pretreatment session. At this dose the quarter-life value decreased from a control value of 77% to a value of 50%. When LAAM (10.0 mg/kg) was administered either 3 or 6 hr prior to the initiation of the session, the drug tended to increase the low rates of responding observed under the FI, while the higher rates were either decreased or remained unchanged. In addition, when the 3 mg/kg dose of LAAM was given 6 hours prior to the session, the effects of the drug also were dependent upon the pre-drug rates of responding. All other injections of LAAM failed to show rate-dependency as indicated by a lack of negatively-sloped regression lines. The LAAM-induced decreases in rates of responding under the FR component of the multiple schedule were the result of increased pausing after reinforcement which was often followed by complete loss of FR responding later in the session (Fig. 2).

Figure 3 shows the dose-effect curve for LAAM on locomotor activity, which is expressed as percent of the control injection. It is apparent that LAAM produced marked increases in locomotor activity when administered at doses of 1 mg/kg and 3 mg/kg. These increases occurred within 1 hour for the 3 mg/kg injection and within 6 hr for the 1 mg/kg injection. These doses produced peak increases in locomotor activity 7 hr after injection. After a dose of 10 mg/kg, LAAM produced a slight decrease (93% of control) in average locomotor activity over the entire 10 hour period. However, the greatest decreases in locomotor activity were observed between 3 and 7 hr after LAAM's administration.

DISCUSSION

The behavioral effects of LAAM show a gradual onset and long duration of action. These two characteristics of LAAM differ sharply from the very rapid onset and short duration of action seen with both morphine and methadone. Administration of these two narcotics at similar dose levels will decrease rates of responding under both components of a multiple FI FR schedule when given immediately prior to the initiation of the session [20, 21, 32]. In contrast to these immediate effects, LAAM gradually decreased rates of responding under both components of the multiple schedule as

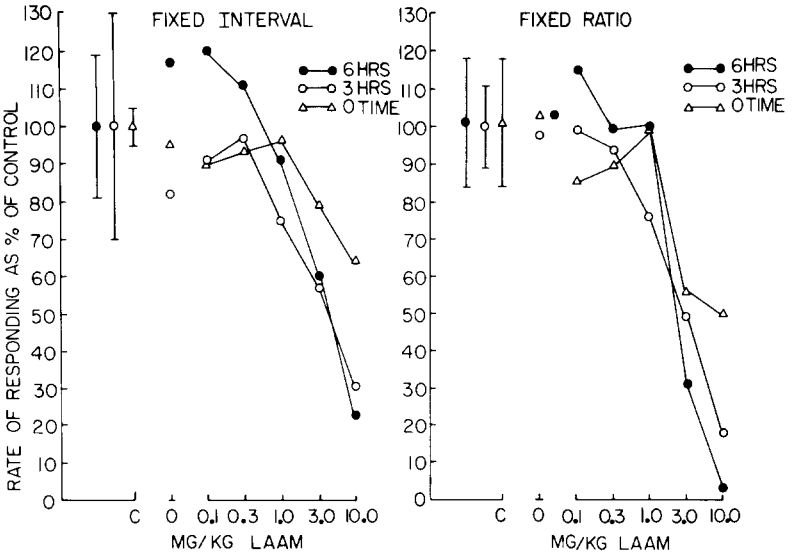

FIG. 1. Effects of varying doses of LAAM on FI FR responding at different times after administration of the drug. Abscissa: doses of LAAM, log scale. Ordinate: average rates of responding expressed as % of control rate. The point and brackets above C represent the mean ± 1 SD for control rates of responding. The symbols at 0 show the effect of distilled water injections. Control and distilled water values represent 3 determinations for each of the 3 male rats. Symbols are as follows: △ (0 time); ○ (3 hr pretreatment); ● (6 hr pretreatment).

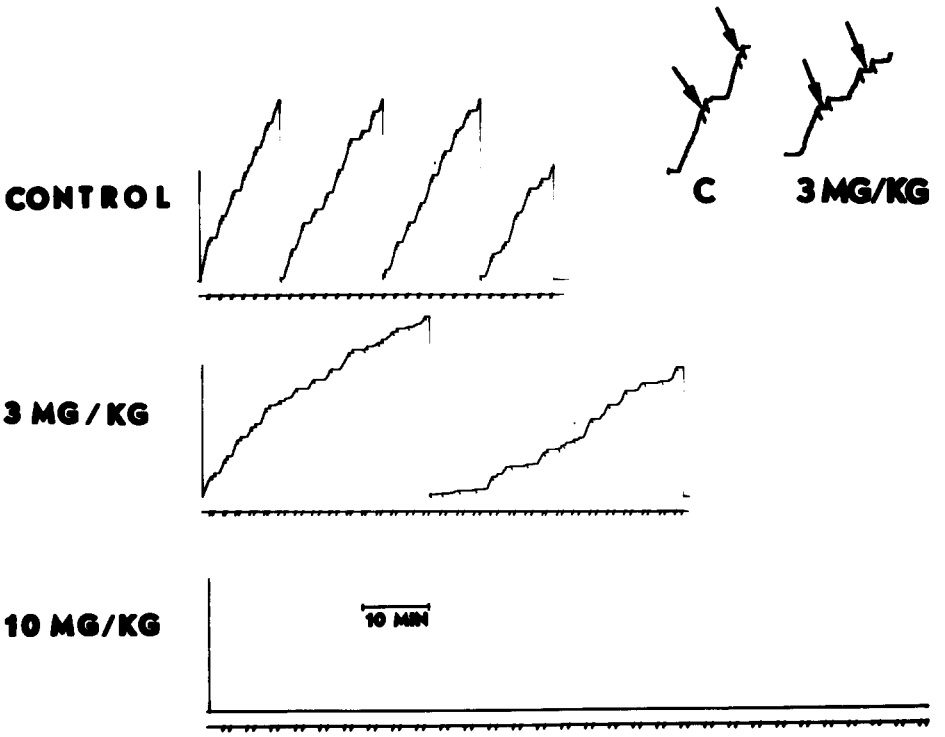

FIG. 2. Representative cumulative records of lever pressing under a multiple FI 90-sec FR 10-response schedule of food presentation. Abscissa: time. Ordinate: cumulative number of responses. Each lever press drives the pen upward and the pen resets after 550 responses. Pen deflections indicate reinforcement under either component of the multiple schedule. On the bottom line, pen deflections represent a change in the schedule component. The records show performances under the multiple schedule for control, 3 mg/kg LAAM, and 10 mg/kg LAAM sessions, when LAAM was administered 6 hr prior to the initiation of the session. The inset shows the increased pausing under the FR component after reinforcement for the 3 mg/kg session as compared to the control session.

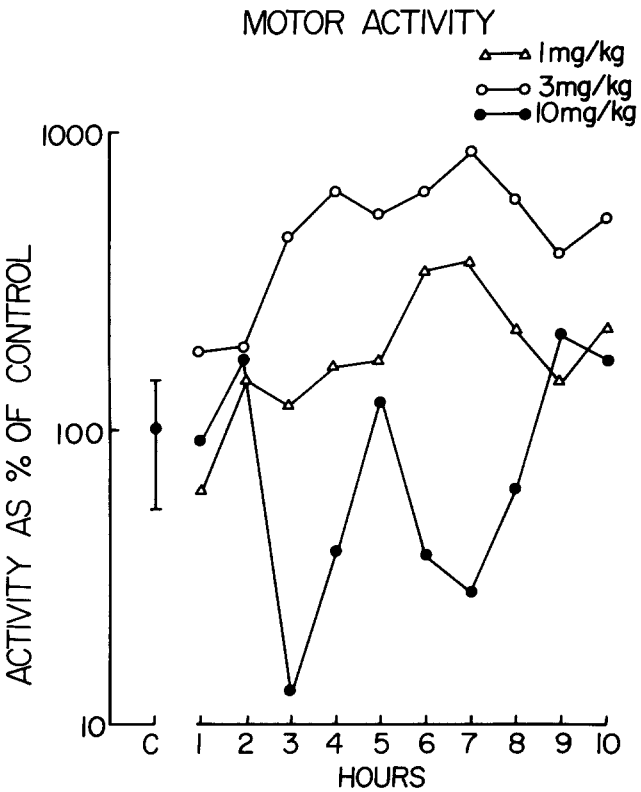

FIG. 3. Effects of varying doses of LAAM on locomotor activity levels of 4 male rats over a 10 hr period. Abscissa: hourly intervals after administration of the drug. Ordinate: activity expressed as % of control average hourly activity, log scale. The point and brackets above C represent the mean ± 1 SD for activity levels during control distilled water injections. Symbols are as follows: △ (1 mg/kg); ○ (3 mg/kg); ● (10 mg/kg).

the interval between administration of the drug and initiation of the session was increased. The lack of any rate-increasing effects under the FI component of the multiple schedule contrasts with its effects on locomotor activity and with the rate-increasing effects on FI responding seen after administration of morphine in rats [29] and after morphine [20] and methadone [21] administration in pigeons.

Quarter-life values which describe patterns of responding under the FI component of a multiple schedule were altered at a dose of 10 mg/kg and only for the 6-hr pretreatment interval. Thus, while LAAM at 3 mg/kg (3- and 6-hr pretreatments) and 10 mg/kg (3-hr pretreatment) decreased the rates of responding under the FI component of the multiple schedule, quarter-life values were unchanged. In contrast, other narcotics such as morphine [20], methadone [21] and meperidine [19] have been shown to produce marked decreases in quarter-life values at several dose levels.

Doses of 1 mg/kg and 3 mg/kg LAAM produced hyperactivity which peaked 7 hours after administration of the drug. The increased activity produced by the 3 mg/kg dose was evident within the first hour and lasted throughout the ten hour session. Similar increases in locomotor activity have been demonstrated with other narcotics such as morphine and methadone [4, 5, 25]. One study [25], in particular, described an "explosive" motor behavior after intraventricular infusion of morphine. However, the increases in locomotor activity produced by LAAM persisted for greater periods of time than the hyperactivity observed after either morphine or methadone administration.

The 3 and 6 hr dose response curves of LAAM for schedule-controlled responding are similar to the 0 hour dose response curves for morphine and methadone [21,29] with respect to the dose-dependent rate-decreasing effects. These rate-decreasing effects and the prolonged hyperactivity produced by LAAM demonstrate that, while the onset of action of LAAM is more gradual than that of other narcotics, LAAM's behavioral effects are as marked as those seen with morphine and methadone and are much longer in duration. Therefore, while LAAM offers advantages for the prolonged suppression of narcotic withdrawal symptoms, it also possesses the potential to cause extended behavioral effects in drug naive individuals, if channeled into the illicit drug market.

The long duration of action of LAAM has been ascribed to the transformation of the drug to a more active metabolite and to LAAM's tendency to bind to plasma protein and/or tissue binding sites [13, 15, 27]. It has been reported that the N-demethylation of LAAM to levo-alpha-noracetylmethadol (N-LAAM) increases the affinity of the compound for the opiate receptor [14]. Also, N-LAAM has been shown to be 6–8 times more potent than LAAM in producing analgesia in mice after subcutaneous administration [28]. Previous metabolic studies have demonstrated that peak brain [27] and plasma [15] levels of LAAM and N-LAAM occurred 2 hours after oral administration of the parent compound to rats and mice respectively. Brain concentrations of LAAM in the rat then steadily declined to a level approximately 25% of the 2 hr peak (140 ng eq/g). N-LAAM brain levels decreased to approximately 55% of the 2 hr peak (36 ng eq/g), however by the eighth hour, a secondary peak of N-LAAM occurred in brain, which was approximately 70% of its 2 hr level. The peak brain and plasma concentrations of LAAM and, especially, N-LAAM observed in these metabolic studies correlate with the marked decreases in responding which occurred under both components of the multiple schedule 3 and 6 hr after administration of the drug. Also, the secondary peak of N-LAAM found in the metabolic studies correlates with the time course of LAAM's largest effect on locomotor activity which occurred in the 7–8 hr interval. These observations suggest that the active metabolites of LAAM, particularly N-LAAM, may contribute to the drug's behavioral effects, which become greater with time, and also to the long duration of action of LAAM.

Analysis of LAAM's effects on schedule-controlled responding and locomotor activity suggests that, although the behavioral effects of the drug become greater with time, the potency of LAAM is close to that of morphine and methadone [21, 29, 32]. The present study also extends the long duration of LAAM's action, previously observed in studies on analgesia [2] and on suppression of narcotic withdrawal symptoms [16], to the drug's effects on schedule-controlled responding and locomotor activity.

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