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Behavioral Effects of Chronic Oral Administration of *levo*-alpha-Acetylmethadol in the Rat[1]

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AIGNER, T. G. AND R. L. BALSTER. *Behavioral effects of chronic oral administration of* levo-*alpha-Acetylmethadol in the rat.* PHARMAC. BIOCHEM. BEHAV. 8(5) 593–596, 1978. – *levo*-alpha-Acetylmethadol was orally administered via a sucrose solution to rats in their drinking water for 24 days. A control group received only sucrose. Body weight and fluid consumption were monitored daily. The behavioral effects during chronic drug administration and during eight days of withdrawal were studied using behavior controlled by a fixed-interval schedule of food reinforcement. Body weights of treated animals remained stable during drug administration but decreased by approximately 25% during withdrawal. There were no significant differences in volume of fluid consumed by the two groups. Response rate and number of reinforcements were decreased during drug administration. During withdrawal, response rates were greater than pre-drug control rates.

levo-alpha-Acetylmethadol Fixed-interval Oral administration Withdrawal

LEVO-ALPHA-ACETYLMETHADOL (LAAM) is a synthetic congener of methadone. Compared to methadone and morphine, LAAM has been reported to have a slow onset and extended duration of opioid actions in animals [2,3] and in man [5,9]. Like methadone, LAAM is effective when administered orally. Fraser and Isbell [5] studied the effects of LAAM in humans and reported LAAM's ability to prevent opiate withdrawal symptoms for up to 72 hr. Unlike morphine, the abrupt withdrawal of LAAM was reported to cause a prolonged, but mild abstinence syndrome. Because of this profile of pharmacological actions, interest has been generated for the use of LAAM as a therapeutic alternative to methadone [8]. However, certain questions concerning the effects of prolonged administration of LAAM have not been examined. For example, there have been few reports on the behavioral effects of extended LAAM treatment.

Schedule-controlled behavior has proven to be a useful technique in studying various drug effects in animals. Its applicability to studying diverse classes of drugs has been well documented. Recently, these techniques have been successfully applied to the study of the behavioral effects of the morphine withdrawal syndrome in the rat [1,4] and in the monkey [6].

Several investigators have reported that under certain conditions, rats will voluntarily drink narcotic solutions in their drinking water in sufficient quantities to induce signs of abstinence after abrupt withdrawal or following an injection of the narcotic antagonist, naloxone [10–13]. The method of oral LAAM administration has the possible advantage of reducing fluctuations in blood levels following widely spaced acute injections. In addition, oral administration more closely parallels the human use situation.

The present investigation was undertaken to determine if rats would drink LAAM solutions, and if so, whether in sufficient quantities to develop physical dependence. Behavioral measures concurrent with the drug administration regimen were also examined with the objective of identifying and possibly quantifying changes during extended LAAM administration.

METHOD

The animals used were 11 naive Sprague-Dawley rats weighing 125–150 g at the start of the experiment. A state of food deprivation sufficient to motivate food-reinforced operant behavior was obtained by free feeding the animals in their home cage for one hr immediately after each experimental session. During the experiment various fluids were available in the animals' home cages. A standard 8 oz water bottle was suspended outside the cage with a standard licking tube (Wahmann, LC-312) projecting through the mesh cage wall.

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Prior to the initiation of drug administration, the animals were trained to lever press in a standard operant chamber (Coulbourn). The chamber was housed in a ventilated, sound attenuating enclosure. The reinforcer was a 45 mg Noyes food pellet automatically dispensed into a food trough centered in the front of the chamber. Solid-state behavioral programming equipment was located in an adjacent room. A fixed interval 90 sec (FI 90) schedule of reinforcement was used. On this schedule, the first lever press to occur following a 90 sec interval resulted in the delivery of a single food pellet. Each daily experimental session was 30 min in duration. During this training period all animals had water available ad lib in their home cages.

After responding had stabilized (approximately 20 days), monitoring of daily fluid intake was begun. The rats were randomly divided into an experimental group (N = 6) and a control group (N = 5). For the first eight days, both groups received a 5% sucrose solution in their home cage as their only source of fluid. Following this period, drug administration was begun. On Days 1–8 of drug administration, the experimental group received LAAM (0.05 mg/ml) dissolved in the sucrose solution. On Days 9–24, the concentration of LAAM was increased to 0.10 mg/ml. On Days 25–32 the drug group once again received only the sucrose solution. The control group received only the sucrose solution throughout the study. Corrections for spillage and evaporation as suggested by Kumar and Stolerman [11] were carried out. Body weight and fluid consumption were monitored on a daily basis with both measures being recorded at approximately 9:00 a.m. each day. Daily experimental sessions were begun approximately one hr later.

LAAM was obtained from the National Institute on Drug Abuse. The concentrations of LAAM were calculated in terms of the hydrochloride salt.

RESULTS

Mean daily fluid intake volumes for both experimental and control groups are presented in Table 1. With the exception of Days 30 and 31 during withdrawal, there were no significant differences between drug and control groups. All of the rats in the experimental group drank the LAAM solution without incident and at volumes comparable to pre-drug levels. No attempt was made in the present study to determine if rats would voluntarily drink LAAM solutions without sucrose. Since there were no differences in fluid intake between groups or between pre-drug and drug periods, the present vehicle system was considered satisfactory.

Figure 1 shows the mean body weights for the experimental and control groups. During the 24 days when LAAM was administered via the drinking water, the average weight of the rats in the experimental group remained stable. During this same time period, the average weight of the control group steadily increased. Following the removal of LAAM from the drinking water on Day 25, the drug group demonstrated approximately a 25% loss in weight for Days 26, 27, and 28. During this three day period, the effects of this large weight loss were readily evident in the appearance of the animals. Diarrhea, wetdog shakes, and hyperirritability were seen in a majority of the animals; however, no systematic rating of withdrawal symptoms was carried out. Following the period of initial weight loss, the average weight of the drug group increased to near control group weight.

TABLE 1

MEAN TOTAL DAILY FLUID INTAKE FOR DRUG AND CONTROL GROUPS (VALUES ARE IN ML/KG/DAY ± SEM)

Solution	Day	Drug Group	Control Group
5% Sucrose	1–8	206 (10)	206 (7)
5% Sucrose + 0.05 mg/ml LAAM	1–8	199 (20)	208 (21)
5% Sucrose + 0.10 mg/ml LAAM	9–16	230 (29)	187 (6)
	17–24	216 (24)	183 (12)
5% Sucrose	25	157 (33)	190 (10)
	26	204 (27)	182 (8)
	27	192 (36)	188 (12)
	28	208 (13)	193 (12)
	29	209 (13)	186 (6)
	30	247 (9)*	188 (8)
	31	244 (20)*	179 (10)
	32	218 (11)	181 (9)

*Significantly different from control ($p \leq 0.05$)

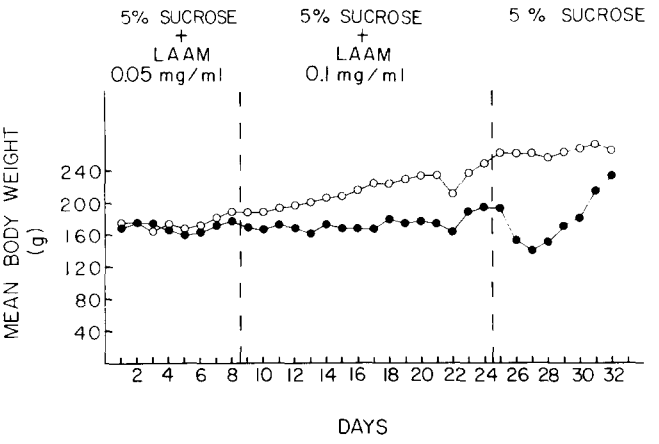

FIG. 1. Mean body weights for the group drinking LAAM + sucrose (closed circles, N = 6) and the control group drinking sucrose alone (open circles, N = 5).

Figure 2 shows the mean daily drug intake (mg/kg/day) for the experimental group. Although daily intake was somewhat variable, substantial amounts of LAAM were consumed over the later portion of this chronic regimen, averaging between 15 and 25 mg/kg/day. There was no significant alteration in fluid intake between Days 8 and 9 when the concentration of LAAM was increased from 0.05 to 0.10 mg/ml.

Figure 3 shows the results of the behavioral mea-

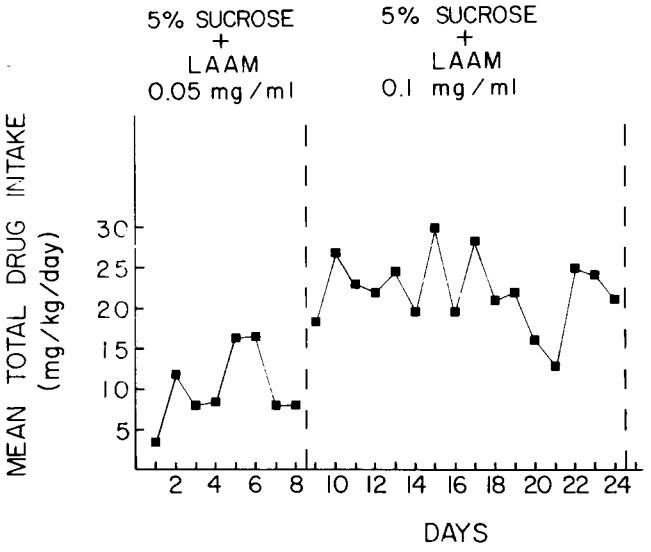

FIG. 2. Mean total daily drug intake for the experimental group during the 24 days of oral LAAM administration.

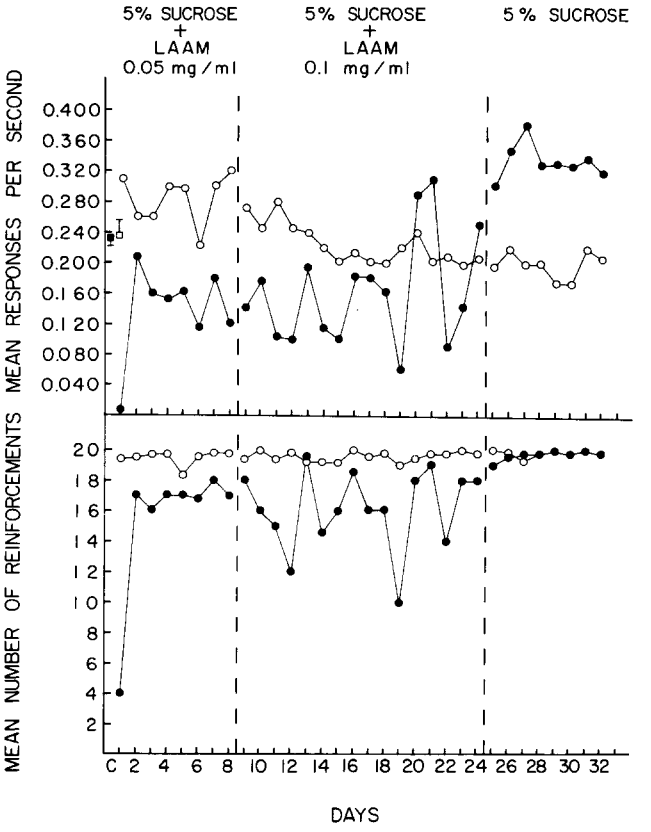

FIG. 3. Upper panel: Mean response rate for sucrose control group (open circles) and LAAM + sucrose group (closed circles). Pre-drug control rates (± SEM) for control (open square) and experimental (closed square) groups are indicated at C. Lower panel: Mean number of reinforcements per session for control (open circles) and experimental (closed circles) groups.

surements. The lower panel shows the mean number of reinforcements obtained in each session. A maximum of 20 pellets was possible for each session. The control group received near the maximum number of pellets throughout the study. The drug group exhibited a wide variability in the number of reinforcers received. Only after termination of the drug administration did this group receive a maximal number of reinforcers in each session. The upper panel in Fig. 3 shows the mean response rate per session for both groups. The drug group responded at a lower rate throughout the treatment period and then exhibited a marked rate increase following withdrawal of LAAM.

DISCUSSION

LAAM can be effectively administered in the drinking water of rats in such a manner as to induce physical dependence. In the present study, rats drinking a LAAM-sucrose solution over a 24 day period evidenced signs of weight loss upon abrupt discontinuation of the drug from the solution. The extent of the weight loss in the present study is in general agreement with results from previous reports [7,11] demonstrating physical dependence of the morphine type in rats. The results also provide evidence of the quantity of LAAM which can be orally administered to rats over an extended period. Although the body weights of the rats given LAAM were considerably less than the body weights of the control group, the drug group remained in good health throughout the study.

Recent reports have suggested that schedule-controlled behavior may be an additional method for quantifying the severity of the morphine abstinence syndrome. Ford and Balster [4] reported the effects of morphine withdrawal following a 21 day chronic IP administration regimen on lever pressing behavior in rats performing a differential reinforcement of low rate (DRL) schedule. These authors reported a five day withdrawal syndrome which produced a biphasic effect on response rates. Decreases in rates early in withdrawal were followed by increases in rates later in withdrawal. In the present study, abrupt withdrawal of LAAM was followed only by response rate increases and an accompanying increase in the number of reinforcements. This increased response rate continued for the 8 days measured following drug withdrawal. At no time was there evidence of a rate-decreasing effect as reported by Ford and Balster for morphine. Babbini, et al., [1] also reported only increases in FI response rates in rats withdrawn from chronic morphine injection. These results suggest the importance of the schedule in determining the withdrawal effects of narcotics on responding.

In the present study, it is difficult to find much evidence of behavioral tolerance development to the effects of LAAM on lever pressing during chronic administration. While there was a marked improvement from Day 1 to Day 2, it is difficult to describe this effect as tolerance development. The Day 1 session was started approximately 1–2 hr after the initial exposure to LAAM in the drinking water. Since the rats were not water deprived, there is little reason to suspect a greater initial drug intake for that session. Indeed, total drug intake (Fig. 2) for Day 1 was less than that for the other sessions. We are uncertain to what to attribute the marked effects on operant behavior seen on Day 1. Although they may have been acute drug effects, they may also have been related to the introduction of a novel solution in the home cage only hours before the

session. The data from Day 2 essentially represent the results of the first 24 hr per day access to LAAM. Following the severe depressant effect on Day 1, the drug group's performance throughout the treatment period continued to be below pre-drug control levels, and was far more variable than controls. These results suggest that behavioral tolerance did not develop or was developing slowly. There was also little tendency shown by the animals to increase their drug intake during this period, although this may have been due to regulation of fluid consumption. This apparent lack of tolerance development may have been due to an accumulation of LAAM or its metabolites, although further studies which are better designed to study this question are needed.

In conclusion, the present study has demonstrated the usefulness of the oral administration technique as a method for inducing physical dependence to LAAM in rats. The simultaneous use of behavioral methods shows promise for elucidating chronic effects of LAAM when administered for more extended time periods. More detailed studies on the behavioral effects of LAAM regarding tolerance development and withdrawal should add more needed information to our knowledge of the actions and applications of this drug.

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