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BRIEF COMMUNICATION

levo-alpha-Acetylmethadol and Metabolites: Some Effects on Schedule-Controlled Behavior in the Rat[1]

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AIGNER, T.G., R.D. FORD AND R.L. BALSTER. levo-*alpha-Acetylmethadol and metabolites: Some effects on schedule-controlled behavior in the rat.* PHARMAC. BIOCHEM. BEHAV. 8(6) 735–737, 1978. – The behavioral effects of acute IP administration of l-α-acetylmethadol, its metabolites, l-α-noracetylmethadol and l-α-dinoracetylmethadol, and morphine were studied in the rat using behavior controlled by a fixed-interval schedule of food reinforcement. Administration of all compounds produced a dose-related decrease in response rate. The metabolites were approximately three to four times the potency of the parent compound which was approximately five times the potency of morphine. Data obtained from cumulative response records suggested that the onset of effects for the metabolites was more rapid than for the parent compound.

Morphine *levo*-alpha-Acetylmethadol Fixed-interval schedule Metabolism Operant behavior

LEVO-ALPHA-ACETYLMETHADOL (LAAM) is a synthetic derivative of methadone. This compound is currently being investigated as a possible alternative to methadone in the therapy of opiate dependence [7]. LAAM has been shown to have a slow onset and long duration of narcotic actions in animals [2,3] and in man [6,8]. Such activity is suggestive of metabolism to a more active form. Metabolism studies [1,9] in the rat have shown LAAM to be progressively N-demethylated to *levo*-alpha-noracetylmethadol (NAM) and to *levo*-alpha-dinoracetylmethadol (NNAM). The opioid-like activity of these metabolites in various tests has been reported [1,11]. However, there have been no published studies of the behavioral effects of these compounds.

Schedule-controlled behavior has been shown to be a sensitive indicator of various effects of a wide range of drugs in several animal species. The present study was undertaken to examine the relative effects of LAAM and its metabolites on schedule-controlled behavior in the rat. These effects were compared to the prototype opiate, morphine.

METHOD

Animals

Twelve naive male Sprague-Dawley rats weighing between 200 and 250 g at the start of experimentation were used. They were food deprived and maintained at approximately 80% of their free-feeding weight. Except for the time spent in the experimental chamber, rats were individually housed with free access to water. A light–dark cycle of 12 hr each was maintained throughout the study.

Apparatus

A standard operant chamber (Coulbourn) with a single response lever was used. A force of approximately 15 g constituted a response. The reinforcer was a 45 mg Noyes food pellet automatically dispensed into a food trough centered in the front of the chamber. Sound attenuation was accomplished by placing the chamber in a ventilated enclosure. Solid-state behavioral programming equipment was located in an adjacent room.

Procedure

Rats were trained to lever press on a fixed interval 90 sec (FI90) schedule. On this schedule, the first response to occur following a 90 sec interval resulted in reinforcement by a single food pellet. Daily session durations were 3 hr.

Drug Procedure

LAAM, NAM, and NNAM in the form of the hydro-

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chloride salts were obtained from the National Institute on Drug Abuse. Morphine sulfate was obtained commercially. All drugs were dissolved in normal saline for injection and the doses are expressed in terms of the salt. A dose-response curve consisting of three doses was obtained for each of the four drugs. In addition, saline vehicle injections were tested in each animal. A volume of 1 ml/kg of the test compound was injected IP 5 min prior to the test session.

The animals were randomly divided into three groups for the study. Group I received only LAAM, Group II received NAM and NNAM, while Group III received only morphine. Drug doses and vehicle were administered in an unsystematic order with at least three non-drug control days intervening between each test dose. For Group II, two animals received the three doses of NAM followed by the three doses of NNAM. The order of testing was reversed for the other two animals. The effects of each drug for each animal were calculated as the percent change from the mean of the three preceding baseline days for that animal. These derived values were then averaged for each dose comparison. In general, only three baseline days intervened between dose determinations. Data for the day after testing high doses of each compound often reflected incomplete recovery and were not considered in calculating baseline values.

RESULTS

Characteristic patterns of responding during an FI schedule of reinforcement [4] were evidenced by each rat. While the response rates across sessions were stable within animals, a certain amount of interanimal variability was evidenced. In spite of this interanimal variability, non-drug baseline mean response rates between groups were not appreciably different. The baseline response rates (± SEM) for each group were as follows: Group I: 0.139 (0.028); Group II: 0.097 (0.003); and Group III: 0.106 (0.006) responses per second.

Figure 1 presents the effects on FI performance of the four drugs, each tested at three doses, as well as the results of the saline vehicle control injections. This data represents the acute effects of each drug during a 3 hr session. For all drugs, a dose related decrement in response rate is evident. Linear regression analysis of this dose-effect data was calculated in order to arrive at potency estimates. Doses which decreased baseline response rates by 50% (ED50) were claculated in terms of the base for each drug. The ED50's (mg/kg) for these four drugs were as follows: NAM, 0.56; NNAM, 0.75; LAAM, 2.14; and morphine, 10.72. Both of the metabolites were approximately 3–4 times more potent than LAAM which was 5 times more potent than morphine in decreasing FI response rates.

Although hour by hour response totals were not recorded, evidence from the cumulative records tended to support the suggestion that the activity of LAAM is due to an active metabolite. Approximate measurements were made from the cumulative records in order to compare the distribution of responses between the first and second halves of the 3 hr session. The percent of the total responses occurring during the first half of the session was determined. These values were averaged for the four rats at each dose determination and are presented in Table 1. A delayed onset of action would be reflected in a greater percentage of responses in the first half of the session. A more rapid onset of action could be reflected in two ways:

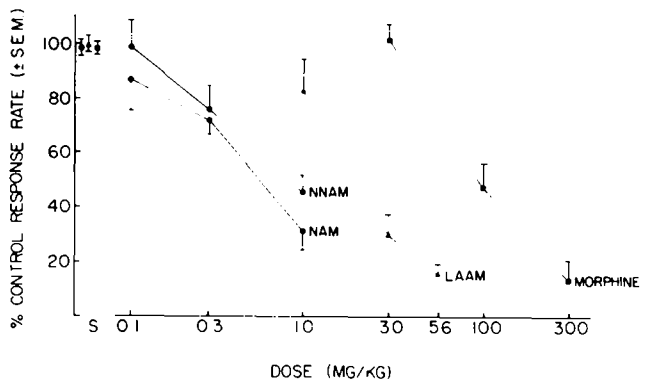

FIG. 1. The effects of morphine, LAAM, NAM, and NNAM on FI performance.

TABLE 1

MEAN PERCENTAGE OF RESPONSES OCCURRING DURING THE FIRST HALF OF THE THREE HOUR SESSION

Morphine		LAAM		NAM		NNAM	
dose*	%	dose*	%	dose*	%	dose*	%
3.0	38	1.0	79	0.1	53	0.1	50
10.0	43	3.0	82	0.3	50	0.3	50
30.0	64	5.6	85	1.0	56	1.0	56

*mg/kg of salt

either an equal amount of response suppression throughout the 3 hr session or greater disruption in the first half indicative of recovery before the end of the session. These results show that LAAM had a greater effect during the last 1-1/2 hr of the 3 hr session indicating a slower onset of action than NAM or NNAM.

DISCUSSION

Acute administration of LAAM, NAM, NNAM, and morphine resulted in a dose related decrement in response rate. These results with NAM and NNAM confirms previous reports [1,11] that the principle metabolites of LAAM have activity and extend these actions to behavioral measures. The relative potencies of LAAM and morphine in the present study are in general agreement with previous reported values in various test procedures. Wax [12] reported LAAM to be approximately 6 times as potent as morphine in the tail-pinch procedure at three and one-half hr following subcutaneous administration. In the present study, the response rate decreases indicated LAAM to be approximately five times more potent when compared to the response rate decreases produced by morphine. The potency of morphine in the present study is in agreement with previous reports [5,10].

Nickander *et al.* [11] reported that both NAM and NNAM were approximately 15 times as active as LAAM as measured in vitro by the opiate-like agonist effects on the isolated guinea pig ileum. In the present study, the two metabolites were approximately 3–4 times more potent than LAAM in decreasing response rates. This difference in results is consistent with the proposed role of metabolism of LAAM to a more active compound in vivo. For both of the metabolites, the distribution of responses was evenly

distributed between the first and second halves of the 3 hr session. The results with LAAM tended to indicate that a greater percentage of responses occurred during the first half of the session, suggesting a delayed onset of drug effects. For the 3.0 and 10.0 mg/kg doses of morphine, a slightly lesser percentage of total responses occurred during the first half of the session, indicating some recovery from the drug effects by the end of the 3 hr session.

In conclusion, the present study has demonstrated the comparative effects of LAAM and its metabolites on schedule-controlled responding in the rat. The applicability of the FI90 schedule in studying behavior for extended time periods necessary for drugs with delayed onset and extended durations of action such as LAAM has also been demonstrated.

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