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Modification of Drug Effects by *l*-α-Acetylmethadol[1]

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McMILLAN, D. E. AND M. BROCCO. *Modification of drug effects of l-α-acetylmethadol.* PHARMACOL BIOCHEM BEHAV 20(4) 543–546, 1984.—The effects of drugs on rate of responding by rats under a multiple fixed-ratio fixed-interval schedule of food presentation were studied before and during chronic administration of *l*-α-acetylmethadol (LAAM). Small doses of methadone, phencyclidine, chlordiazepoxide and pentobarbital increased rates of responding under the fixed-interval-component of the schedule. At higher doses, these drugs, as well as LAAM, morphine and haloperidol, decreased rates of responding under both schedule components. Chronic LAAM administration shifted the dose-effect curves for LAAM, morphine, methadone, and to some extent, perhaps pentobarbital, to the right, but did not shift the dose-effect curves to the right for chlordiazepoxide, phencyclidine and haloperidol. The rate-increasing effects of small doses of methadone, phencyclidine, pentobarbital and chlordiazepoxide were attenuated during chronic LAAM administration.

l-α-Acetylmethadol Drug interaction

l-α-ACETYLMETHADOL (LAAM) has been considered as an alternative to methadone in the maintenance treatment of former heroin addicts. Both LAAM and methadone produce cross tolerance and cross dependence to the opioid drugs, which presumably is the basis for their clinical usefulness [1].

In previous experiments, we have observed some interesting drug interactions during the chronic administration of methadone and LAAM. In the rat, with methadone given chronically in the drinking water, little tolerance occurred to the effects of intraperitoneal methadone injections on rates of responding for food under a multiple fixed-ratio fixed-interval schedule; however, the morphine and pentobarbital dose-effect curves shifted to the right in these animals [6]. The failure of the dose-effect curve for racemic methadone to shift was confirmed for the *l*-isomer when *l*-methadone was given chronically (Raitano and McMillan, 1983). However, in other experiments, chronic administration of LAAM, or methadone, produced tolerance to their respective effects on schedule-controlled responding in pigeons [5].

Methadone maintenance patients frequently abuse other drugs, or require the use of other drugs for legitimate therapeutic reasons [4,9]. Therefore, it is important to determine the interaction between chronic administration of methadone or LAAM and other drugs. The purpose of the present series of experiments was to study the effects of chronic administration of LAAM on the effects of other drugs on the schedule-controlled behavior of the rat.

METHOD

Subjects

The subjects were 8 male Sprague Dawley rats weighing between 320 and 370 g when given free access to food and water. Four rats were used to study the effects of chronic LAAM administration on the behavioral effects of LAAM, chlordiazepoxide, pentobarbital and haloperidol and the other four rats were used to study the effects of chronic LAAM administration on the behavioral effects of LAAM, morphine, phencyclidine and methadone. The rats were given a reduced food supply until they reached 80% of the free-feeding weight. Throughout the experiments they were maintained at these reduced weights.

Apparatus

The chambers were Gerbrands operant conditioning chambers housed in sound attenuating enclosures. Noyes rat pellets (94 mg) could be dispensed into Gerbrands food receptacles centered in the stimulus panel of the test chamber. Gerbrands rat levers were mounted on the right and left sides of the test panel. Only the left lever was active. Lever presses and food pellet deliveries were recorded on cumulative recorders and digital counters. Programming and recording equipment were housed in a separate room from the test chambers.

Drugs

The drugs studied were *l*-α-acetylmethadol hydrochloride (LAAM), chlordiazepoxide hydrochloride, sodium pentobarbital, haloperidol hydrochloride, morphine sulfate, phencyclidine hydrochloride and methadone hydrochloride. Dose levels were calculated as the salts. LAAM was dissolved in distilled water. All other drugs were dissolved in physiologic saline. Both distilled water and physiologic

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saline were given as vehicle controls. When dose-effect curves were determined, drugs and vehicles were administered intraperitoneally.

Injections were given at various times before the test session as follows: LAAM: 2 hr; chlordiazepoxide and pentobarbital: 15 min; haloperidol, morphine, phencyclidine and methadone: 5 min.

Procedure

Rats were trained to lever press by successive approximations. After lever pressing was established, responding was maintained under a multiple fixed-interval, 5-min, fixed-ratio 30-response (mult FI FR) schedule with two red lights above the left lever during the FR component and 2 white lights above each lever during the FI component. A 20-sec timeout period in total darkness separated the two components. Lever presses during the timeout had no programmed consequences. A 90-sec limited hold applied to the FI component and a 60-sec limited hold applied to the FR component, so that the FI component terminated 90 sec after the 5-min interval if no response occurred and 60 sec after the beginning of the FR component if 30 responses had not occurred. Otherwise, the schedule components terminated with food delivery. Each session consisted of 12 alternating presentations of each component beginning with the FR component.

Rats were trained under the multiple schedule for about 6 weeks, then dose-effect determinations began. Dose-effect curves for LAAM, chlordiazepoxide, pentobarbital and haloperidol were determined in 4 rats. Dose-effect curves for LAAM, morphine, phencyclidine and methadone were determined in the other 4 rats. Drug injections were given on Tuesdays and Fridays, while Thursdays served as vehicle injection control days. Some animals received an ascending dosage series and other animals were given the doses in a mixed order. Furthermore, in order to avoid any tolerance development, one week separated two successive test sessions with morphine, LAAM or methadone.

After determination of the dose-effect curves, chronic LAAM administration began with an oral administration of 1 mg/kg immediately after the session for 5 days. Subsequently, the maintenance dose of LAAM was increased to 3 mg/kg for 10 days and 5.6 mg/kg for 10 days, after which dose-effect curves were redetermined with 5.6 mg/kg LAAM continuing to be given daily after the test session. Dose-effect curves were determined in the same order as before the chronic treatment with LAAM. The total duration of chronic oral LAAM administration was 10 weeks.

After 6 weeks without chronic LAAM treatment, the effects of selected doses of LAAM and methadone were redetermined.

Data Analysis

The mean rate of responding in each group was calculated by averaging the individual data obtained under the same treatment conditions. Control data were obtained during sessions after the administration of the vehicle on Thursdays.

Drug effects obtained before and during chronic treatment with LAAM were compared to the control data of the corresponding phase of the study. Differences between drug and control data were considered to be significant when the mean rate of responding after drug was more than 2 standard deviations from the mean control rate.

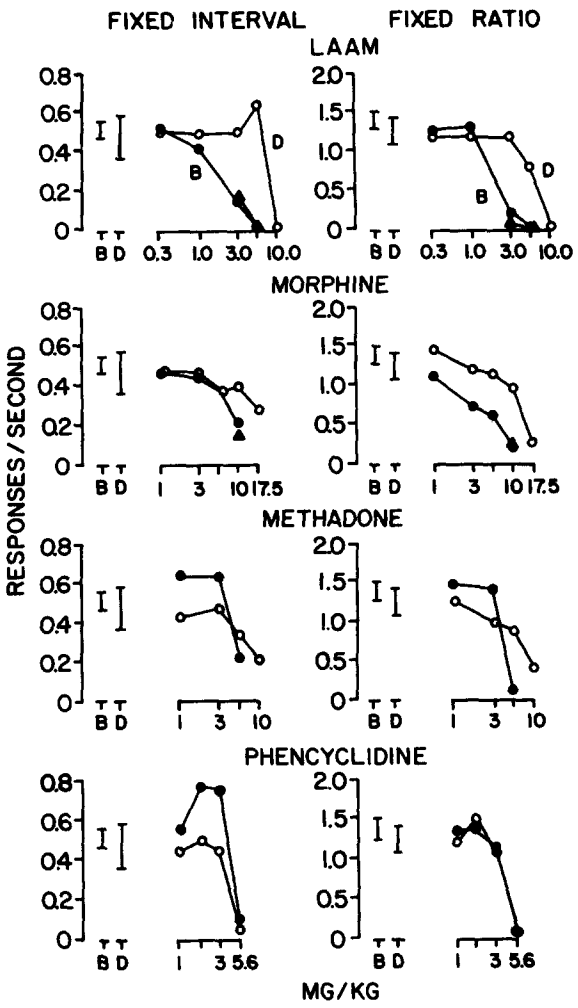

FIG. 1. Effects of LAAM, morphine, methadone and phencyclidine on rates of responding before (B, ●), during (D, ○) and in some cases, after (▲) chronic post-session administration of LAAM. Abscissa: dose, log scale. Ordinate: rate of responding during an entire session in responses/sec. Brackets show ±2 standard deviations around the control mean. Each point is a mean of single observations in each of 4 rats. The descending leg of the dose-effect curve for fixed-ratio responding before chronic LAAM administration was significantly shifted to the right during chronic LAAM administration for LAAM, morphine and methadone, but not for phencyclidine.

The complex shape of the dose-effect curves before and during chronic LAAM administration made statistical comparison of these curves difficult. Therefore, no statistical tests were performed on the curves for fixed-interval responding; however, shifts in the descending leg of the dose-effect curve for fixed-ratio responding were analysed by subjecting the dose-effect curves to an analysis by the signed ranks test using paired observations across doses [2].

RESULTS

Figure 1 shows the effects of LAAM, morphine, methadone and phencyclidine before (●) and during (○) chronic, oral, post-session administration of LAAM. Prior to chronic oral administration of LAAM, intraperitoneal injections of LAAM and morphine produced dose-dependent de-

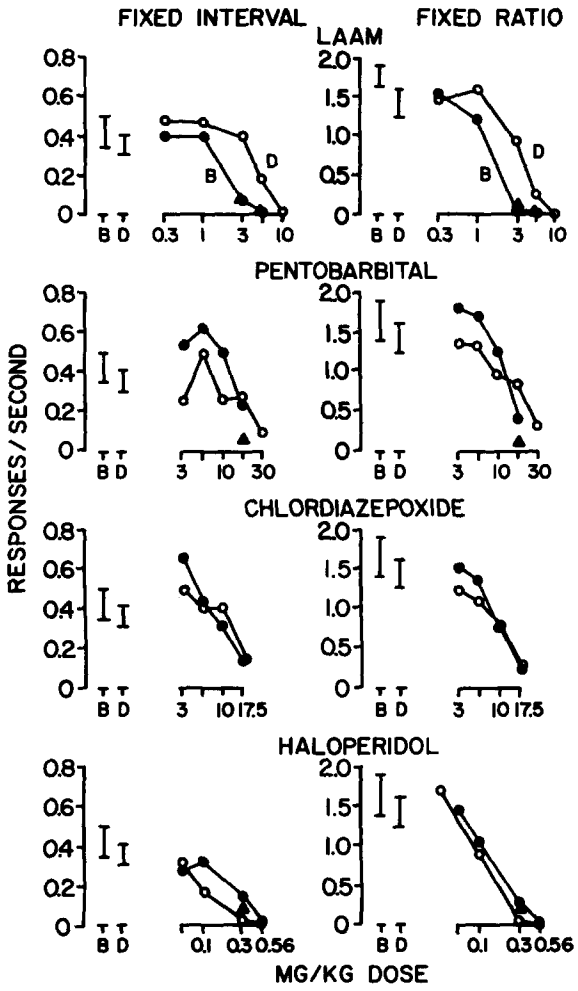

FIG. 2. Effects of LAAM, pentobarbital, chlordiazepoxide and haloperidol on rates of responding before (B, ●), during (D, ○) and in some cases, after (▲) chronic post-session administration of LAAM. Abscissa: dose, log scale. Ordinate: rate of responding during an entire session in responses/sec. Brackets show ±2 standard deviations around the control mean. Each point is a mean of single observations in each of 4 rats (only 3 rats are shown for haloperidol due to the death of one rat before completion of the dose-effect curve). Only the LAAM dose-effect curve shifted significantly during chronic LAAM administration.

creases in rates of responding under both schedule components. Methadone and phencyclidine produced small rate increases under the FI component of the schedule at low doses while higher doses decreased the rate under both schedule components.

During chronic administration of LAAM, the dose-effect curves for LAAM, morphine and methadone were shifted significantly to the right. The rate-increasing effect of methadone on fixed-interval responding was attenuated. Although chronic administration of LAAM also attenuated the rate-increasing effect of phencyclidine, the phencyclidine dose-effect curves were not shifted to the right.

After 6 weeks without chronic LAAM administration, the effects of selected doses of LAAM and methadone were redetermined (▲). The points fell very close to the values obtained at these drug doses prior to chronic LAAM administration.

Figure 2 shows the effects of LAAM, pentobarbital, chlordiazepoxide and haloperidol on responding under the multiple schedule before and during chronic oral post-session LAAM administration. LAAM and haloperidol produced dose-dependent decreases in rates of responding under both schedule components prior to chronic LAAM administration. Low doses of chlordiazepoxide and pentobarbital increased rates of responding under the FI component of the schedule, while higher doses decreased under both schedule components.

Chronic oral LAAM administration shifted the dose-effect curve for LAAM to the right, just as had occurred in the other group of rats. There was a tendency for the pentobarbital dose-effect curve also to shift to the right, especially under the FR component, although the effect was not statistically significant. Chronic LAAM administration attenuated the rate-increasing effect of pentobarbital and chloridazepoxide. Chronic LAAM administration had little effect on the rate decreasing effect of chloridazepoxide. The haloperidol dose-effect curve was shifted slightly to the left for FI component, although the shift failed to meet statistical significance.

When chronic LAAM administration was discontinued for 6 weeks and then selected doses of some of the drugs were studied again, the LAAM points (▲) fell very close to those of the original dose-effect curve. Pentobarbital had even greater depressant effects after chronic LAAM administration than those obtained prior to chronic LAAM administration, while the effects of haloperidol fell between the dose-effect curves determined before and during LAAM administration.

Thus, tolerance appears to develop to LAAM. There is cross tolerance to methadone, morphine and possibly pentobarbital, but not to phencyclidine and chlordiazepoxide. There may be a slightly increased sensitivity to the effects of haloperidol, although the shift was not statistically significant.

DISCUSSION

Our experiments demonstrate that tolerance develops in rats to the effects of LAAM on schedule-controlled behavior. Furthermore, there is cross tolerance from LAAM to morphine, methadone and perhaps pentobarbital, but not to phencyclidine, chlordiazepoxide or haloperidol.

We have observed previously that the chronic administration of LAAM to rats produces tolerance to the effects of LAAM on schedule-controlled responding [5], but we have been unsuccessful in developing tolerance to the effects of methadone in rats, using similar procedures [6,7]. Although tolerance to the effects of methadone could not be demonstrated, chronic methadone clearly had effects since the morphine dose-effect curve in these same rats shifted to the right during chronic methadone administration.

LAAM has a longer duration of action than methadone, presumably due to its conversion to active metabolites [2,3]. Perhaps the persistance of active metabolites during chronic LAAM administration produces the development of a greater degree of tolerance to LAAM and cross tolerance to methadone than the degree of tolerance that develops with chronic methadone administration. There are two problems with this suggestion. First, the morphine dose-effect curve shifted to about the same degree during chronic LAAM administration in the present study as it did when methadone was given chroni-

cally [6,7]. If LAAM simply produced a greater degree of tolerance than methadone, why was this not reflected in the degree of shift of the morphine dose-effect curve? Secondly, the failure of methadone to produce tolerance on repeated administration is closely related to the behavior measured, since tolerance clearly develops to the effects of methadone on spontaneous motor activity [7,10].

There was only a slight suggestion of cross tolerance from LAAM to pentobarbital in the present experiments. Methadone appears to produce a cross tolerance to the effects of pentobarbital on schedule-controlled behavior [6]. Cross tolerance from methadone to pentobarbital may result in part from a more rapid metabolism of pentobarbital in rats treated chronically with methadone [8]. LAAM may also induce pentobarbital metabolism. It is not likely that cross tolerance from LAAM to pentobarbital would occur because of pharmacodynamic cross tolerance from LAAM to non-opioid CNS depressants, since cross tolerance between LAAM and either phencyclidine or chlordiazepoxide was not observed for rate-decreasing effects.

In summary, these experiments show that animals tolerant to LAAM show a cross tolerance to the effects of other opioids on schedule-controlled behavior and possibly to pentobarbital. No cross tolerance from LAAM to the effects of phencyclidine, chlordiazepoxide or haloperidol on scheduled-controlled behavior was observed.

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