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Electric Shock Titration: Effects of Meperidine, Anileridine and Alphaprodine[1]

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DYKSTRA, L. A. AND J. D. LEANDER. *Electric shock titration: effects of meperidine, anileridine and alphaprodine.* PHARMAC. BIOCHEM. BEHAV. 8 (4) 387–389, 1978. – The effects of meperidine, anileridine and alphaprodine were studied in the squirrel monkey whose behavior was maintained under a 2.0-sec schedule of shock increment. Low doses of all three drugs had no effect, whereas higher doses decreased responding at the zero shock intensity. Slightly higher doses of meperidine and anileridine increased responding at the zero shock intensity and produced convulsions.

Titration Meperidine Anileridine Alphaprodine Electric shock

MEPERIDINE, a phenylpiperidine-derived narcotic, and morphine are both used clinically as analgesics although there are a number of qualitative differences between these two drugs. For example, meperidine produces effects at high doses which are dissimilar to those produced by high doses of morphine. These effects include convulsions and other signs of central nervous system stimulation such as hyperreflexia and tremors [5]. The narcotic antagonists, nalorphine and naloxone, do not antagonize these effects, and chronic administration of meperidine does not lead to tolerance to these effects [3, 7, 10]. It has been suggested that some of these effects may be due to the fact that one metabolite of meperidine is the convulsant normeperidine [1].

In view of these differences between morphine and meperidine, it is interesting to determine whether the effects of these two drugs are also dissimilar in situations designed to investigate their analgesic properties. Whereas the analgesic effects of morphine have been examined in a number of situations, meperidine's effects have been examined less extensively. One procedure which has been used to assess the analgesic effects of morphine is the shock titration procedure. In this procedure morphine increases the level at which both rats and monkeys maintain an electric shock under a variety of conditions [2, 9, 12, 13]. It has also been reported in one study that meperidine increases the level at which rhesus monkeys maintain an electric shock under a shock titration procedure [9].

The present study employs this procedure to examine further the effects of meperidine as well as two other phenylpiperidine derivatives: anileridine and alphaprodine. Clinically, anileridine is more potent than alphaprodine which is more potent than meperidine. Alphaprodine's duration of action is markedly shorter than that of anileridine or meperidine [5]. Anileridine, like meperidine, is converted to normeperidine [8], whereas alphaprodine is not.

METHOD

Animals

Three adult male squirrel monkeys (*Saimiri sciureus*) were housed individually and maintained at free-feeding weights (700–900 g). All monkeys had continuous access to water and were given 8–10 Purina Monkey Chow biscuits and a vitamin C tablet every day. In addition, their diet was supplemented with fresh fruit.

Apparatus

Monkeys were restrained in a chair similar to the one described by Hake and Azrin [4]. Electric current was delivered to the tail by two hinged brass plates which rested lightly on a shaved portion of the tail. The electric shock was 100 V a.c., 60 Hz, delivered to the plates through a series resistance of about 180 K ohms. The shock intensity was adjusted through a series of potentiometers. A response key was mounted on the right side of the front panel facing the monkey. The entire chair unit was enclosed in a ventilated sound-attenuating chamber. See Dykstra and McMillan [2] for further details of the procedure.

Behavioral Procedure

A schedule of continuous electric shock presentation was employed. The shock intensity increased in 20 increments from 0 to 5.0 mA in 0.25 mA steps. Shock was on continuously and its intensity increased by one increment (0.25 mA) every 2.0-sec. Each response reduced

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shock intensity by 0.25 mA. Sixty min experimental sessions were conducted Monday through Friday.

Drugs

Doses of meperidine hydrochloride, anileridine dihydrochloride and alphaprodine hydrochloride were all calculated as the salt and dissolved in water. Water was used for vehicle injections. Drugs were given in mixed order, and doses of each drug were generally given in ascending and descending order. Injections were made into the leg muscle in a volume of 1.0 ml/kg of body weight. Following drug administration, monkeys were returned to their home cages for 20 min. Injections were generally given every Tuesday and Friday with Thursday serving as a non-injection control day. There was no evidence that tolerance developed with this schedule of drug administration.

Data Analysis

Rates of responding were measured for the entire 60-min experimental session. The number of responses which occurred at each shock intensity was also recorded.

RESULTS

On non-injection control days, most responses occurred at the zero and the 0.25 mA shock intensities. The shock intensity never increased beyond 0.50 mA in any monkey. Meperidine, anileridine and alphaprodine all altered the number of responses which occurred at the zero shock intensity, but produced little or no change in responding at the higher shock intensities. The highest intensity which the monkeys allowed the shock to reach was not increased by any drug. Figure 1 presents the number of responses which occurred at the zero shock intensity following control injections and following meperidine, alphaprodine and anileridine.

Intermediate doses of meperidine decreased the number of responses which occurred at the zero shock intensity in all three monkeys. Higher doses increased responding at the zero shock intensity in monkeys No. 2 and No. 4, and a slightly higher dose of meperidine produced convulsions in these monkeys within a few minutes of administration. These convulsions could not be reversed by naloxone, but they were reversed by diazepam. In monkey No. 8 higher doses of meperidine either decreased responding at the zero shock intensity or produced severe sedation and respiratory depression which completely eliminated responding.

The effects of anileridine were similar to those of meperidine. In monkeys No. 2 and No. 4, low doses of anileridine had no effect, a higher dose decreased the number of responses which occurred at the zero shock intensity, and a slightly higher dose increased the number of responses at the zero shock intensity. An even higher dose produced convulsions which could be reversed by diazepam, but not by naloxone. In monkey No. 8, anileridine only decreased responding at the zero shock intensity or produced severe sedation such that responding was eliminated and the experimental session terminated.

Alphaprodine decreased responding at the zero shock intensity in all three monkeys, up to a dose at which the monkeys stopped responding entirely and their respiration was decreased.

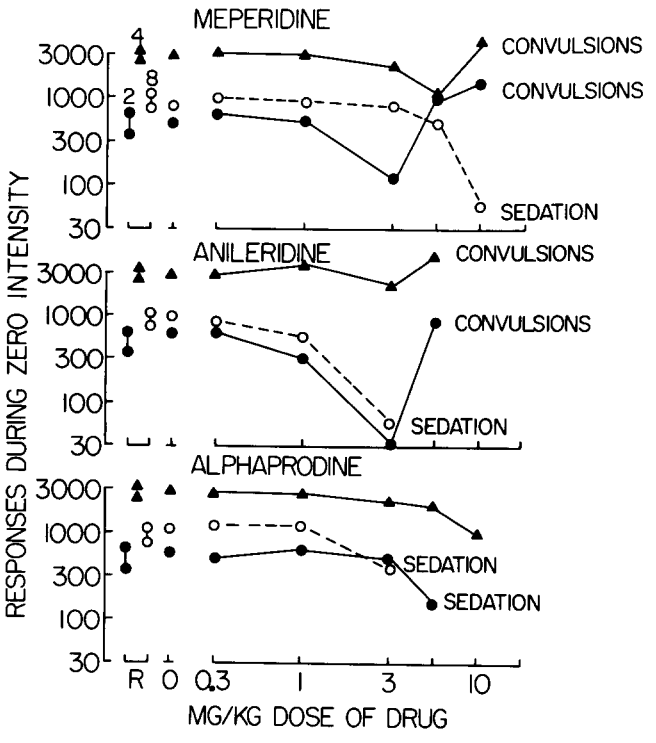

FIG. 1. Effects of meperidine, anileridine and alphaprodine on responses during the zero shock intensity under a shock titration schedule in three monkeys. Abscissa: milligrams per kilogram, log scale. Ordinate: number of responses during the zero shock intensity during the entire session (log scale). The brackets at R represent the range of control values (Thursdays) in each monkey. Points at 0 show the effects of control injections. ●———●, ▲———▲, o- - - -o are dose-response curves for monkeys No. 2, No. 4 and No. 8, respectively. Each point is the mean of two injections in each monkey.

DISCUSSION

The results show that no dose of meperidine, anileridine or alphaprodine changed the maximally tolerated shock under the shock-titration procedure; however, selected doses of these drugs altered the number of responses which occurred at the zero shock intensity. In two of the three monkeys, intermediate doses of meperidine and anileridine decreased and higher doses increased the number of responses at the zero shock intensity and produced convulsions. In the third monkey, these drugs only decreased the number of responses at the zero shock intensity and produced sedation at high doses. Alphaprodine decreased the number of responses at the zero shock intensity in all three monkeys.

The effects of meperidine, anileridine and alphaprodine under the titration procedure are different from those usually reported in squirrel monkeys for other narcotic analgesics. In a procedure identical to the one examined here, morphine (1.0–3.0 mg/kg), methadone (1.7 mg/kg), and pentazocine (10 mg/kg) decreased the number of responses which occurred at the zero and the 0.25 mA shock intensities, and they also increased the highest intensity which the shock was allowed to reach [2].

These data suggest that there are qualitative differences in the squirrel monkey between meperidine and other narcotic analgesics. Whereas these drugs all alter responding when no shock is present (i.e., at the zero shock intensity), meperidine, anileridine and alphaprodine do not alter responding in the presence of shock.

Another notable feature of the data reported here is the difference between the effects of high doses of meperidine and anileridine and the effects of high doses of alphaprodine. In monkeys No. 2 and No. 4, high doses of meperidine and anileridine increased the number of responses which occurred at the zero shock intensity, and even higher doses produced convulsions. On the other hand, alphaprodine did not increase responding at the zero shock intensity in any monkey; moreover, high doses of alphaprodine produced sedation and respiratory depression rather than convulsions. The differences seen following high doses of alphaprodine and high doses of meperidine and anileridine may be related to the fact that both meperidine and anileridine are metabolized to normeperidine which is a convulsant [1,8], whereas alphaprodine is not converted to normeperidine. Moreover, there is evidence that the squirrel monkey is more capable of forming normeperidine than are other species [11]. The fact that convulsions did not occur following meperidine and anileridine in monkey No. 8 may be related to the fact that this monkey differed from the other two monkeys in a number of observable features. Of the three types of squirrel monkeys that have been described [6], monkey No. 8 fits the description of the roman arch phenotype, whereas monkeys No. 2 and No. 4 fit the description of the gothic arch phenotype.

It also should be noted that the convulsions produced by high doses of meperidine and anileridine could not be antagonized by naloxone whereas the sedation and respiratory depression produced by high doses of alphaprodine were antagonized by naloxone. Others have also reported that many of the effects of high doses of meperidine are not blocked by administration of narcotic antagonists [3, 7, 10].

In conclusion, the effects under a titration procedure of meperidine, anileridine and alphaprodine are different from those reported for morphine and other narcotic analgesics. Meperidine, anileridine and alphaprodine do not increase the intensity which a shock is allowed to reach under the titration procedure as morphine does. Moreover, high doses of meperidine and anileridine have effects which cannot be antagonized by a narcotic antagonist.

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