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Interactions Between Naloxone and Narcotic Analgesics under Three Schedules that induce Polydipsia[1]

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MCMILLAN, D. E. AND J. D. LEANDER. *Interactions between naloxone and narcotic analgesics under three schedules that induce polydipsia.* PHARMAC. BIOCHEM. BEHAV. 5(2) 195–200, 1976. – A pattern of schedule-induced polydipsia was maintained in rats by a fixed-time schedule where food pellets were presented every 90 sec, a fixed-interval schedule where licking the drinking tube produced pellets every 90 sec, or a fixed-interval schedule where lever presses produced pellets every 90 sec. Under all 3 schedules, injections of morphine, methadone, etonitazene and meperidine generally decreased licking rates and amounts of water consumed, as well as rates of lever-pressing under the schedules where lever presses were required. Naloxone (1 mg/kg) almost completely blocked the effects of morphine and etonitazene, but the effects of methadone sometimes were blocked to a lesser degree. Small increases in the rate of licking and amount of water consumed after the lowest dose of meperidine under the schedule requiring lever-presses were blocked by naloxone, but the higher doses of meperidine that decreased licking, lever-pressing and amount of water consumed under the three schedules were not blocked by naloxone. These data suggest that there are important differences in the ability of naloxone to antagonize the behavioral effects of different narcotic analgesics.

Naloxone Polydipsia Narcotic analgesics

FALK [2] first reported that rats would consume excessive amounts of water when small food pellets were presented on an intermittent schedule (Schedule-induced polydipsia). A number of publications [3, 11, 16, 20], including some from this laboratory [8, 9, 10, 13, 14], have adapted versions of Falk's technique to induce animals to ingest drug solutions. Despite the frequent adaptation of schedule-induced polydipsia to the study of drug ingestion, only a few investigators have reported the acute effects of drug injections on the excessive water consumption produced by schedule-induced polydipsia [9,12]. The major purpose of the present experiments was to study the acute effects of several narcotic analgesics on patterns of water consumption under 3 variations of Falk's technique that we have used to induce ingestion of some of these same narcotic analgesics [8, 9, 10, 13]. Because of some interesting differences among narcotic analgesics in the degree to which their behavioral effects in pigeons are blocked by narcotic antagonists [7,15], the interaction between naloxone and these narcotic analgesics also was studied.

METHOD

Animals

Sprague-Dawley rats approximately 120 days old at the start of the experiments were used. Body weights were maintained at approximately 300 g by food pellets delivered during test sessions and by postsession supplemental feeding. Tap water was freely available in each rat's home cage, except for 24 hr before the first training session.

Apparatus

The test cages were Lehigh Valley Electronics or Gerbrands rat test chambers housed in sound attenuating chambers. Noyes rat pellets (94 mg) could be dispensed into a receptacle centered in the stimulus panel of the test chamber. A Gerbrands rat lever was mounted on the right side of the stimulus panel and on the left side a 1 cm hole allowed access to the drinking tube of an externally mounted water bottle. The drinking tube was recessed 1 cm behind the drinking panel and licks on the tube were recorded with a Grason-Stadler drinkometer. Licks, lever presses and food pellet deliveries were recorded on cumulative recorders and digital counters. The water bottle was weighed before and after each session to determine the amount of water ingested (assuming 1 ml weighed 1 g, with a 1 ml correction for spillage). Programming and recording equipment were housed in a separate room from the test cages.

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Drugs

The drugs studied were morphine sulfate, etonitazene hydrochloride, methadone hydrochloride, meperidine hydrochloride and naloxone hydrochloride. All doses are expressed as these salts. All drugs were dissolved in distilled water and injected intraperitoneally immediately before the session in a volume of 1 ml/kg of body weight. Distilled water was also given as a vehicle control.

Injections usually were given on Tuesdays and Fridays, while Thursdays served as noninjection control days. Dose-effect curves were determined for morphine, methadone, etonitazene and meperidine administered concurrently with distilled-water injections and with 1 mg/kg naloxone injections. For some rats the dose-effect curve for each narcotic was determined with distilled water first, then the dose-effect curve was redetermined with naloxone. For other rats the dose-effect curve for the narcotic was determined with naloxone before it was redetermined with distilled water. Some rats received the narcotics in an ascending dosage series beginning with distilled water (or naloxone) and some in a decending dosage series ending with distilled water (or naloxone). The narcotics were studied in a mixed order, although experiments with a narcotic in the presence of both distilled water and naloxone were completed before experiments with another narcotic were started.

Procedure

Three groups of rats were used. For the first group, pellets were presented 90 sec apart, regardless of the rat's behavior. This schedule of pellet presentation will be referred to as the fixed-time (FT) schedule. A session terminated after 60 pellets had been delivered (90 min). For the second group of rats, pellets were delivered on a lick dependent basis, so that the first contact with the drinking tube after 90 sec had elapsed produced the pellet. This schedule will be referred to as the fixed-interval licking (FI-LK) schedule. A session terminated with the first pellet delivery after 90 min had elapsed. For the final group of rats, lever presses were required to produce food pellets, such that the first lever-press after 90 sec had elapsed, produced the pellet. This schedule will be referred to as the fixed-interval lever-pressing (FI-LV) schedule. A session terminated with the first pellet delivery after 90 min had elapsed.

Rats were tested Monday through Friday. The final reinforcement schedule was in effect at the beginning of the initial session. No attempt was made to train the rats by successive approximations during initial sessions, since lever pressing and/or drinking were readily initiated by all rats. After approximately 25 sessions, performance was considered stable and drug testing began.

RESULTS

Baseline Performance

Figure 1 shows typical cumulative records for baseline performance of rats under each of the 3 schedules. Under the FT schedule, shortly after pellet delivery a sustained high-rate licking episode occurred, which terminated prior to the delivery of the next pellet. Almost every pellet delivery is followed by a similar licking episode.

Under the FI-LK schedule a similar licking episode occurred after pellet delivery (Fig. 1). There is a pause after the post-pellet licking episode, which is followed by a gradually increasing rate of licking which produces the next pellet. Under the FI-LV schedule, the pattern is similar, in that the sustained high-rate licking episode occurs after pellet delivery, and is followed by a short pause; however, the gradually increasing rate of responding that produces the food pellet occurs on the lever under the FI-LV schedule, rather than on the drinking tube as occurred under the FI-LK schedule.

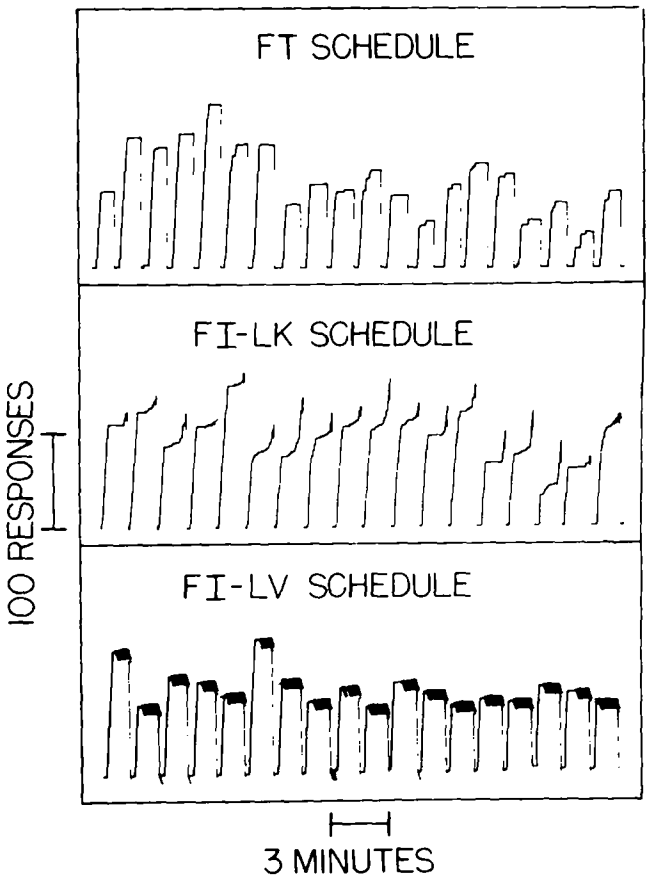

FIG. 1. Representative cumulative records of licking (all frames) and lever-pressing (bottom frame only) under all 3 schedules. Each lick on the drinking tube drives the pen upward. Reset of the pen occurs at delivery of the food pellet. Pen deflections (bottom frame) indicate lever-presses under the FI-LV 90-sec schedule. The records show 30 min segments from 90 min sessions.

Drug Effects

Figure 2 shows rates of licking and volumes of water ingested under the FT schedule after drugs. All 4 drugs produced dose-dependent decreases in both the rate of licking and the volume of water consumed, with decreases in both measures occurring at about the same dose level. The order of potency with both measures was etonitazene > methadone > morphine > meperidine.

The effects of morphine and etonitazene on both licking rate and volume consumed were almost completely blocked by the 1 mg/kg dose of naloxone. This dose of naloxone also blocked methadone-induced decreases in licking rate

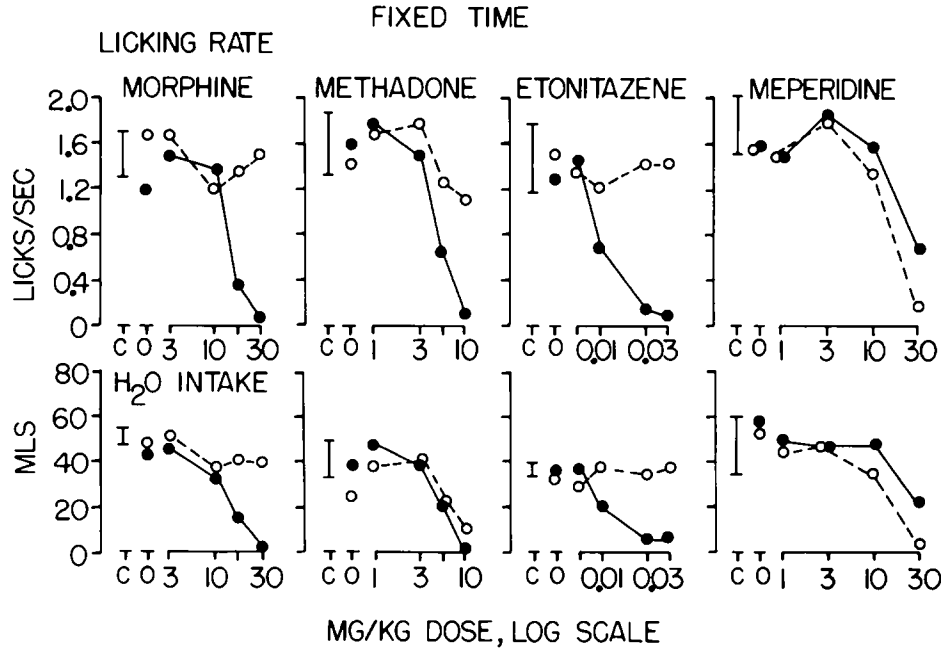

FIG. 2. The effects of narcotic analgesics on licking rate and volume of water consumed under the FT 90-sec schedule. Ordinate: licks on the drinking tube per sec (upper frame) and water intake in mls (lower frame). The brackets at C show ± 2 standard errors of the mean for noninjection sessions (Thursdays), based on at least 5 observations in each of 4 rats. The closed circles at 0 show the effects of distilled water injections and the open circles at 0 show the effects of 1 mg/kg naloxone. The closed circles connected by solid lines show the effects of the narcotics analgesic given concurrently with distilled water. The open circles connected by broken lines show the effects of the narcotic analgesic immediately after 1 mg/kg of naloxone. Each point is the mean of single observations in each of 4 rats.

fairly well, but it did not seem to block the methadone-induced decrease in the volume of water consumed. The effects of meperidine on licking rate and volume consumed were not blocked by this dose of naloxone. In fact, naloxone may have intensified the effects of the highest dose of meperidine.

Figure 3 shows the effects of narcotics on the rates of licking and the water intake under the FI-LK schedule. As under the FT schedule, the narcotics only decreased rates of licking and volume of water intake. Although etonitazene again was by far the most potent drug, methadone was only slightly more potent than morphine and meperidine.

The 1 mg/kg dose of naloxone almost completely blocked the effects of morphine, etonitazene and methadone on both the licking rate and the volume measure; however the meperidine-induced decreases in licking and in the volume of water consumed, again were not blocked by naloxone. In fact, the effects of the highest dose of meperidine again may have been intensified by naloxone.

Figure 4 shows the effects of the four narcotics on rates of lever-pressing, rates of licking and water intake under the FI-LV schedule. Morphine, methadone and etonitazene produced only decreases in rates of lever-pressing and licking and in water consumed. Although meperidine also only decreased rates of lever-pressing, the lowest dose produced small increases in the rate of licking and in the volume of water consumed. Higher doses of meperidine decreased rates of lever-pressing and licking, as well as the volume of water consumed, in a dose-dependent manner. Again etonitazene was most potent, followed by methadone. It was difficult to separate the potencies of morphine and meperidine.

The 1 mg/kg dose of naloxone almost completely blocked the effects of morphine, etonitazene and methadone on lever-pressing, licking and drinking. Although the effects of methadone on lever-pressing appear to have been blocked almost completely by naloxone, the effects of the highest dose of methadone on licking and on the volume of water consumed were only partially blocked by naloxone. Furthermore, low doses of methadone (1 and sometimes 3 mg/kg), which produced little or no effect on lever-pressing, licking and volume of water consumed, produced decreases when combined with naloxone.

The small increases in the rate of licking and the volume of water consumed after 3 mg/kg of meperidine were blocked by 1 mg/kg of naloxone, although this may be related to the rate-decreasing effects of naloxone alone. As in previous experiments, the decreases in lever-pressing rate, licking rate and volume of water consumed were not blocked by naloxone. Again, naloxone seemed to intensify the effects of the highest dose of meperidine on licking rate and the volume of fluid consumed.

DISCUSSION

In these experiments the narcotic analgesics generally decreased rates of licking, rates of lever-pressing and amounts of water consumed under 3 schedules that generate schedule-induced polydipsia. The only exception was that a small dose of meperidine (3 mg/kg) increased

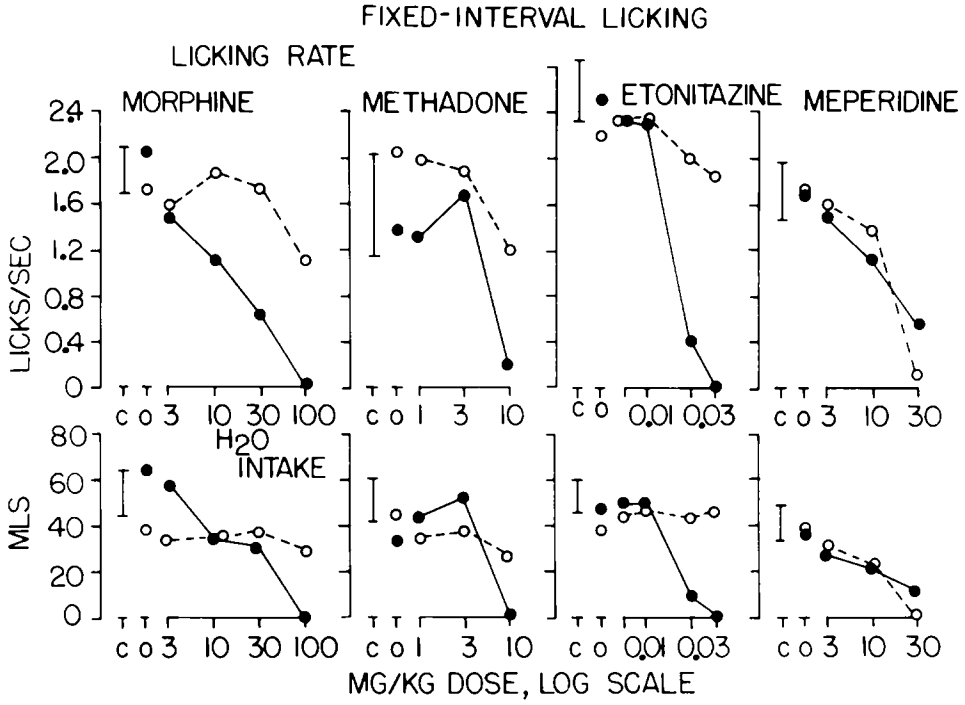

FIG. 3. The effects of narcotic analgesics on licking rate and volume of water consumed under the FI-LK 90-sec schedule of food presentation. Symbols are as in Fig. 2.

rates of licking and the amount of water consumed under the schedule where lever-pressing was required to produce the food pellet. We have previously reported [9] dose-dependent decreases in licking and water consumption following injections of morphine and methadone under this schedule. The reasons for the small increases in the rate of licking and the volume consumed after the lowest dose of meperidine under the schedule that required lever-pressing are not apparent.

Increases in rates of responding under FI schedules occur in pigeons [7,15] for many of these narcotic analgesics. Our failure to find similar increases in FI responding under both the FI-LK and the FI-LV schedules is probably not a species difference, since increases in FI rates after narcotic analgesics have been reported for rats [21,22]. Perhaps it is a function of the size of the fixed interval, or perhaps it related to the polydipsia.

It is well known that naloxone can block a number of the effects of morphine-like narcotic analgesics [6], including those of meperidine [1, 4, 17] and methadone [1, 4, 19]. Thus, it was surprising to find that the rate-decreasing effects of methadone on drinking were not blocked to the same extent as those of morphine and etonitazene and that the rate-decreasing effects of meperidine on behavior were not blocked at all. It is possible that higher doses of naloxone might have blocked the effects of methadone more completely and perhaps blocked the effects of meperidine, yet the dose of naloxone that was used did block the doses of morphine and etonitazene that completely eliminated drinking and lever-pressing. Our data suggest that there may be subtle differences in the behavioral effects of these narcotic analgesics that have not been emphasized previously.

We have reported recently that meperidine increases rates of FI responding by pigeons at low doses and decreases rates of responding at higher doses [7]. The rate increases were blocked by naloxone, but there was no tendency for naloxone to block the rate decreases. These interactions between naloxone and meperidine in pigeons are consistent with these observations in rats. In the one instance where increases were observed (licking and the amount of water consumed under the FI-LV schedule), naloxone blocked the effect, although the block was not impressive since the rate increases were small and naloxone sometimes produced small decreases in behavior when it was given alone. However, when meperidine decreased responding, regardless of the schedule or the measure of behavior used, naloxone failed to block the effects. Recently, it has been reported that naloxone only partially blocks the convulsant effect of meperidine in mice [5]. Thus, the failure of naloxone to block certain effects of meperidine occurs in at least 3 species and with a variety of behavioral measures.

Our data suggest that naloxone may actually have intensified the effects of the highest dose (30 mg/kg) of meperidine. In Fig. 2, 3, and 4, in all 7 instances the combination of naloxone with 30 mg/kg meperidine produced a greater decrease in responding (licking, lever pressing or volume consumed), than was observed when 30 mg/kg of meperidine was given with distilled water. In no instance did the combination of the highest dose of any of the other drugs with naloxone produce a greater decrease in responding than was observed when the drugs were given with distilled water.

Many effects of narcotic analgesics are blocked by narcotic antagonists, but our data suggest that some

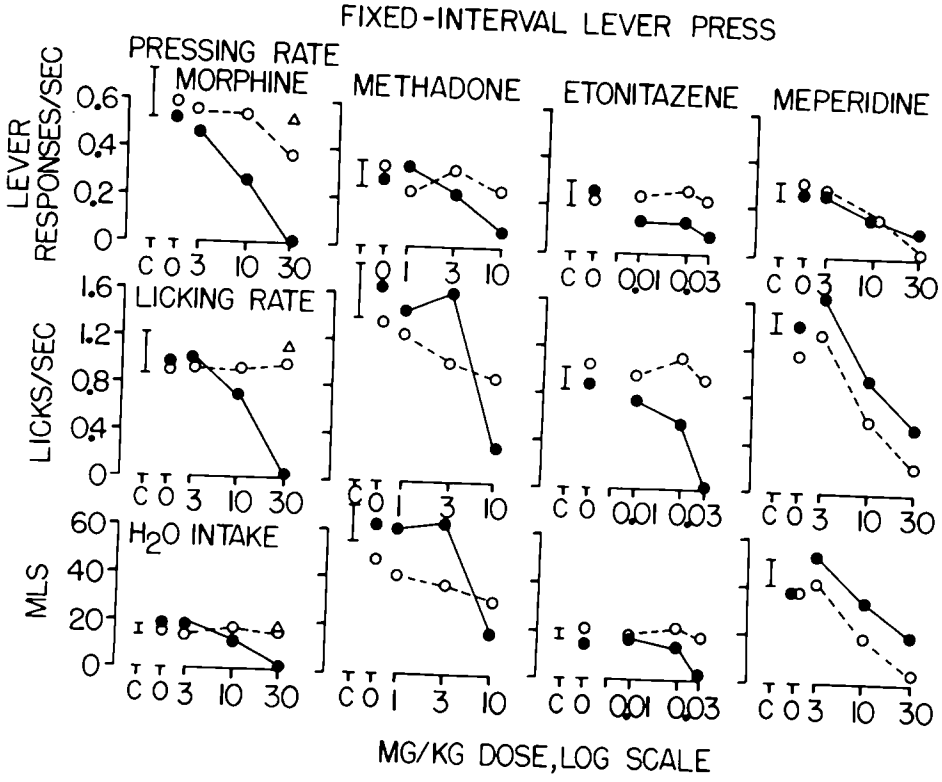

FIG. 4. The effects of narcotic analgesics on lever-pressing rate, licking rate and volume of water consumed under the FI-LV 90 sec schedule of food presentation. Symbols are as in Fig. 2, except that the open triangles show a redetermination of the effects of 30 mg/kg morphine combined with naloxone.

behavioral effects of some narcotic analgesics may not be blocked so easily. With respect to schedule-controlled behavior, whether or not a block occurs may depend on the particular narcotic analgesic under study, as well as upon the behavior measured and the species employed.

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