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Comparison of Morphine, Meperidine, Anileridine, and Alphaprodine on Schedule-Controlled Responding and Analgesia[1]

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LEANDER, J. D. *Comparison of morphine, meperidine, anileridine, and alphaprodine on schedule-controlled responding and analgesia.* PHARMAC. BIOCHEM. BEHAV. 12(5) 797–801, 1980.—The effects of morphine, meperidine, alphaprodine, and anileridine were studied alone and in the presence of 1 mg/kg of naloxone in rats on level pressing under a fixed-ratio 20-response schedule of food presentation and on tail-withdrawal latency from warm water (55°C) as a measure of analgesia. All four narcotics decreased rates of lever pressing and increased tail-withdrawal latencies. Naloxone antagonized the effects of all four narcotics on tail-withdrawal, but did not antagonize the rate-decreasing effect of meperidine on lever pressing. Naloxone shifted the morphine dose-effect for lever-pressing by a factor of 4–8; the alphaprodine dose-effect curve by a factor of 4–8; and the anileridine dose-effect curve by a factor of 2. These results strengthen the interpretation that meperidine's effect on schedule-controlled responding is not mediated by a narcotic action whereas the analgesic effect is. The results also suggest that anileridine has significant non-narcotic actions like meperidine.

Morphine Meperidine Anilerdine Alphaprodine Naloxone Schedule-controlled responding Rats

THE effects of morphine and other narcotics on schedule-controlled behavior have been shown repeatedly to be antagonized by narcotic antagonists such as naloxone, naltrexone, and cyclazocine [3, 4, 10, 16, 19]. An exception to this general statement is the effects of meperidine on the schedule-controlled behavior of pigeons and rats. In pigeons responding under a multiple fixed-ratio, fixed-interval schedule of food presentation, meperidine decreased responding at doses of 10 mg/kg and above [16]. Doses of naloxone from 1 to 30 mg/kg and cyclazocine from 0.1–3 mg/kg were completely ineffective in antagonizing the rate-decreasing effects of meperidine. Likewise, in rats receiving food pellets under 3 different interval schedules of food presentation, meperidine decreased both schedule-induced behavior (adjunctive drinking) and schedule-dependent behavior (drinking or lever pressing) in a dose-related fashion, and naloxone was again ineffective in antagonizing these rate decreases [18]. In contrast, the effects of morphine, methadone, and etonitazene were antagonized by naloxone under all three schedules of food presentation. This lack of antagonism of meperidine's rate decreasing effects by narcotic antagonists has been somewhat surprising since narcotic antagonists are effective in antagonizing the analgesic effects of meperidine in man and various laboratory animals [1, 2, 5, 7].

The effects of two meperidine analogues also have been studied on the responding of pigeons under a multiple fixed-ratio, fixed-interval schedule of food presentation [13]. Naloxone was effective in antagonizing only slightly the rate-decreasing effects of 10 mg/kg of anileridine and alphaprodine, whereas the rate-decreasing, dose-effect curve for fentanyl (a potent narcotic agonist) was shifted by 10–20 fold by the same dose of naloxone. The effects of anileridine and alphaprodine were studied because they are analogues of meperidine and in the same potency range as meperidine. Also, anileridine shares with meperidine the non-narcotic, convulsant metabolite, normeperidine [17], whereas alphaprodine is not metabolized to normeperidine. Normeperidine, like meperidine, produces rate-decreasing effects on schedule-controlled responding which cannot be antagonized by naloxone [14].

The purposes of the present experiment were to evaluate the effects in rats of meperidine, anileridine, and alphaprodine alone and in the presence of naloxone on schedule-controlled behavior and compare the schedule-controlled behavior to the analgesic effects of these drugs. Thus in each rat both the effect on schedule-controlled responding and a measure of analgesia were determined so that a direct comparison could be made in terms of naloxone's ability to antagonize the drug effects on these two behaviors. A secondary purpose was to determine if there were any differences between albino and hooded rats in terms of naloxone's

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TABLE 1
CONTROL DATA

Rat no.	Running weight	Number of control sessions	Mean control (±SD) resp./min	Mean control (±SD) withdrawal latency in sec
Morphine rats (albino)				
61	300 g	10	76.1 (6.1)	2.6 (0.9)
62	300 g	9	75.3 (7.5)	4.0 (1.0)
63	300 g	10	61.1 (12.0)	Lost the terminal portion of tail
64	300 g	8	49.9 (7.3)	3.6 (1.7)
Meperidine rats (albino)				
65	300 g	8	87.5 (18.2)	3.3 (0.7)
66	300 g	7	80.0 (2.3)	4.6 (1.4)
67	300 g	7	53.3 (6.6)	4.0 (1.3)
68	300 g	8	94.9 (11.2)	4.5 (1.1)
Alphaprodine rats (albino)				
47	380 g	13	77.9 (5.6)	3.9 (1.2)
49	380 g	13	99.0 (11.0)	4.2 (1.4)
60	280 g	14	49.3 (10.0)	5.1 (1.2)
74	300 g	10	75.7 (8.3)	3.2 (0.5)
Anileridine rats (albino)				
70	300 g	13	91.2 (11.3)	3.2 (1.1)
71	300 g	12	92.6 (9.1)	2.6 (0.9)
72	320 g	11	70.0 (7.1)	4.5 (0.8)
73	300 g	11	77.0 (3.8)	5.8 (0.8)
Meperidine rats (hooded)				
L-1	300 g	11	63.9 (16.9)	4.8 (1.1)
L-2	300 g	15	65.3 (13.6)	4.9 (0.4)
L-3	300 g	10	67.4 (16.5)	4.1 (0.9)
L-4	300 g	10	55.9 (18.9)	3.8 (1.5)
L-5	300 g	12	80.0 (24.1)	3.0 (1.3)
L-6	300 g	10	54.0 (5.5)	3.1 (1.2)

inability to antagonize meperidine's rate-decreasing effects on schedule-controlled responding.

METHOD

Animals

Sixteen male Sprague-Dawley derived albino rats and six male Long-Evans derived hooded rats obtained from Charles River were used. All rats were approximately 120 days of age at the beginning of the experiments, except for 2, which were considerably older. Running weights were maintained at 300 g (380 g for the two older rats) by food pellets delivered in the test sessions and by postsession supplemental feeding. Tap water was freely available in the home cages.

Apparatus

The test cage measured 25 cm wide, 29.5 cm long, and 28.5 cm high and was housed within a sound and light attenuating, ventilated chamber. Noyes rat pellets (97 mg) could be dispensed into a receptacle in the middle of the front panel of the test cage. To the right of the test cage was a retractable rat lever (Coulbourn), a force of 0.15 N operated the lever and defined a lever press response. During test sessions, a 24 vac house-light illuminated the test cage.

Drugs

The drugs used and the forms in which the doses were calculated are: morphine sulfate, meperidine hydrochloride, alphaprodine hydrochloride, anileridine dihydrochloride, and naloxone hydrochloride. All drugs were dissolved in distilled water and distilled water was administered as control (non-drug) injections. Injections were made intraperitoneally (IP) in a volume of 1 ml/kg of body weight (2 ml for the 80 mg/kg dose of morphine). When interactions of a narcotic with naloxone were studied, both injections were given IP in no deliberate order within 10 sec of each other. In the determination of dose-effect relationships, drug injections were given usually on Tuesdays and Fridays, with Thursdays serving as water-injection control days. Usually, each animal of a group experienced a different order of agonist and naloxone + agonist dose determinations. Injections occurred immediately before being placed in the test chamber.

Procedures

Each test session started with a 10 min time-out in the test chamber, where the houselight was off and lever presses produced no consequences. During the 20 min test session,

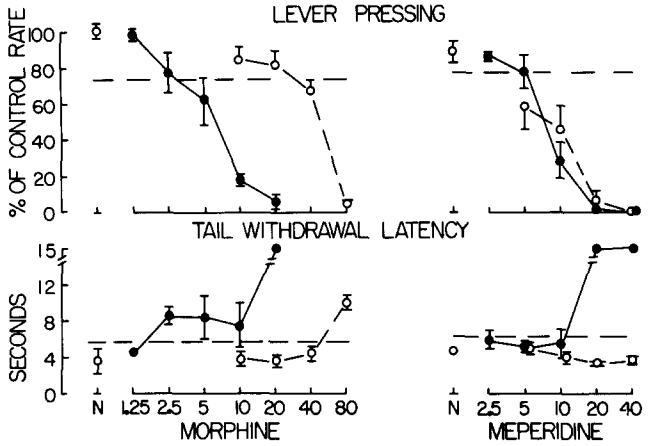

FIG. 1. Effects of morphine (left) and meperidine (right) alone and in the presence of 1 mg/kg of naloxone on rate of lever pressing under a FR 20 schedule of food presentation and on latency to withdraw tail from 55°C water. Ordinate: Upper, rate of responding as a % of each animal's control (non-drug) rate of responding under the FR 20 schedule; Lower, absolute latency in seconds for tail withdrawal. Abscissa, mg/kg dose of drug. The dashed line at approximately 75% of control lever responding indicates 2 standard deviations below the control level of 100%. The dashed line at approximately 6 second of the latency for tail withdrawal indicates 2 standard deviations above the control mean. Any mean point below the dashed line for lever pressing and above the dashed line for latency was considered a significant effect. Each point (and bracket) is the mean (and SEM) of 4 animals. A point without a bracket indicates that the SEM was less than the radius of the point. Filled circles indicate the effects of narcotic agonists alone; unfilled circles indicate the effects of 1 mg/kg naloxone alone (as above N) and effects of the agonists in the presence of 1 mg/kg of naloxone.

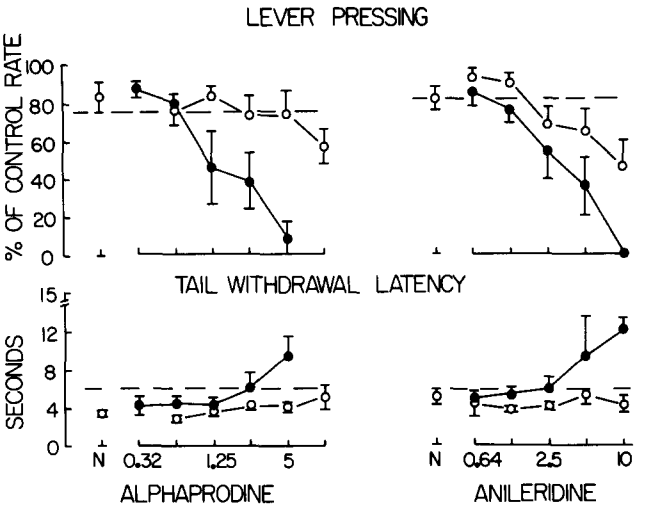

FIG. 2. Effects of alphaprodine (left) and anileridine (right) alone and in the presence of 1 mg/kg of naloxone. Details are similar to Fig. 1.

which was signaled by houselight illumination, each lever press produced an auditory "click" from a feedback relay, and every 20th lever press produced food pellet delivery (FR 20-response schedule of reinforcement) plus a momentary extinguishing of the houselight. All programming and recording equipment were housed in an adjacent room. For individual rats, control rates of lever pressing ranged from 49 to 99 responses/min (Table 1).

The test used to determine the analgesic effects of these drugs was the tail withdrawal reflex induced by application of warm water to the tail [12]. Immediately after the test session ended on drug or water injection days, the rat was removed from the test chamber and placed in a standard rat holder with the tail hanging free outside the holder. The latency for the terminal 5 cm of the rat's tail to be withdrawn from 55°C water was taken as the measure of nociception. If the animal did not remove his tail within 15 sec, the tail was removed from the water by the experimeter and the latency was assigned a value of 15 sec (15 sec cut-off time). Mean control latencies for individual animals ranged from 2.6 to 5.8 sec (Table 1). These data were similar to those in previous reports using this measure of analgesia [12,21].

In a separate time course study of morphine and meperidine, the analgesic effects were comparable at time periods of 10 and 30 min after IP injection. Likewise, the effects of anileridine and alphaprodine appear relatively constant over the time period 10–30 min after IP injection. Thus the fact that in the present study the lever pressing behavior preceded the analgesia measure was not considered to affect the outcome of the study.

RESULTS

Figure 1 shows the effects of morphine and meperidine alone and in the presence of 1 mg/kg of naloxone on lever pressing (schedule-controlled behavior) and on tail-withdrawal (nociception—mediated behavior). Morphine alone produced a significant increase in tail withdrawal latency at 2.5 mg/kg of morphine, and all animals reached the 15 sec cut-off at 20 mg/kg. This dose of morphine alone produced almost complete suppression of lever pressing.

The 1 mg/kg dose of naloxone was used as a maximal narcotic antagonist dose without producing agonist effects of its own. As can be seen in Fig. 1, this dose of naloxone produced a marked shift of the morphine dose-effect curve to the right (by a factor of 4–8) for both the lever-pressing and tail-withdrawal behavior.

The right side of Fig. 1 shows the effects with meperidine. Meperidine alone, at 20 mg/kg, decreased lever pressing to a zero level and produced the analgesic cut-off time (15 sec) in all rats tested. The 1 mg/kg dose of naloxone antagonized the effect of meperidine on the tail-withdrawal behavior, even at 40 mg/kg of meperidine, but had no effect on meperidine's suppressant effect on the rate of lever pressing. In other words, naloxone antagonized the analgesic effects of meperidine but not the suppressant effect on schedule-controlled behavior. It should also be noted that meperidine significantly decreased the rate of lever pressing at a dose (10 mg/kg) which did not produce a significant increase in tail-withdrawal latency.

Figure 2 shows the effects with alphaprodine (left) and anileridine (right) alone and in the presence of 1 mg/kg of naloxone. Both alphaprodine and anileridine produced a dose-related decrease in rate of lever pressing with alphaprodine being twice as potent as anileridine. Like meperidine, both agents significantly lowered rates of lever pressing at lower doses than which increased the tail-withdrawal latency significantly from control. For example, 5 mg/kg of each agent was the lowest dose which clearly increased tail-withdrawal latency, whereas 1.25 mg/kg of each agent significantly decreased rates of lever pressing from the control levels.

The 1 mg/kg dose of naloxone antagonized the effects of both anileridine and alphaprodine on both schedule-controlled behavior and on the tail-withdrawal behavior. However, it does appear that naloxone shifts the alphaprodine dose-effect curve on rates of lever pressing to a greater extent than the anileridine curve. A dose of 10 mg/kg of alphaprodine in the presence of 1 mg/kg of naloxone produced approximately the same decrease as 1.25 mg/kg of alphaprodine alone; in contrast, 2.5 mg/kg of anileridine in the presence of 1 mg/kg of naloxone produced approximately the same decrease as 1.25 mg/kg of anileridine alone.

To evaluate the role of possible strain differences in the effects of meperidine, the effects of meperidine alone and in the presence of 1 mg/kg of naloxone were determined in 6 hooded rats. The data are shown in Fig. 3. The effects in the hooded rats are qualitatively similar to those seen in the albino rats, the only difference being quantitative—it takes approximately twice as much meperidine to produce either suppression of lever pressing or an increase in tail-withdrawal latency in the hooded rat compared to the albino rats. There is not this quantitative difference with morphine; 20 mg/kg of morphine produces virtually complete suppression of lever pressing in both albino and hooded rats (data not shown). As in the albino rats, naloxone at 1 mg/kg was effective in antagonizing the analgesic effect of meperidine in the hooded rat but not the suppression of lever pressing.

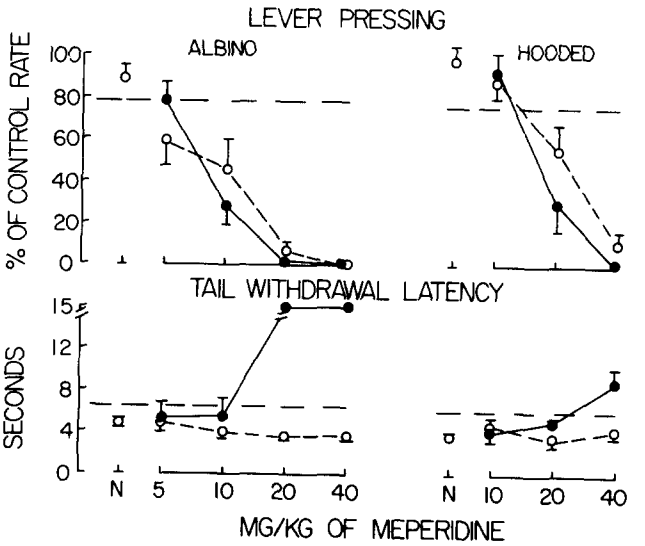

FIG. 3. Effects of meperidine alone and in the presence of 1 mg/kg of naloxone in albino (left) and hooded (right) rats. Details are similar to Fig. 1. Points for hooded rats are the mean (± SEM) of 6. Albino data is repeated from Fig. 1.

DISCUSSION

These results provide a direct comparison of the analgesic effects to the rate-decreasing effects on schedule-controlled responding of meperidine and 2 meperidine analogues, anileridine and alphaprodine. As was predictable from the literature, 1 mg/kg of naloxone antagonized the analgesic effect of meperidine but not the suppression of schedule-controlled behavior produced by meperidine. It was also interesting to note that meperidine significantly decreased rates of lever pressing from control values at lower doses than which were necessary to increase tail withdrawal latency. In contrast, morphine increased tail withdrawal latency at lower doses than which were necessary for significantly decreasing rates of lever pressing. As with meperidine, significant decreases in lever pressing rates were obtained with lower doses of anileridine and alphaprodine than were necessary to significantly increase tail-withdrawal latency. However, unlike the effects of meperidine, the effects of anileridine and alphaprodine on lever pressing were antagonized by naloxone. Like the earlier results in pigeons [13], naloxone appeared to produce on schedule-controlled responding a slightly larger shift of the alphaprodine dose-effect curve to the right than occurred with anileridine. Doses of naloxone greater than 1 mg/kg were not tested as possible antagonists of meperidine because of the greater probability of agonist effects of naloxone such as the decreased food and water intake reported by Holtzman [9], the interactions with drugs not affecting narcotic receptors [8], and because 1 mg/kg is more than adequate to antagonize morphine's effects [20].

In the previous papers on meperidine and related analogues [13, 16, 18], it was hypothesized that the effects of meperidine were a product of two actions. One action was typically narcotic, in that it could be antagonized by naloxone, whereas the second action was a non-narcotic action since it could not be antagonized by naloxone. The present study demonstrates these two actions within the same animals. The analgesic effects were a typical narcotic action whereas the suppression of schedule-controlled behavior was a non-narcotic action. A recent paper shows that the non-narcotic effect of meperidine and normeperidine in the pigeon can be attenuated by pentobarbital [15], which suggests that this non-narcotic effect may be related to the pro-convulsant effects of these agents [6]. The present results showing a smaller shift of the anileridine dose-effect curves than morphine on lever pressing with concurrent naloxone treatment indicates that anileridine also has a significant non-narcotic action which can produce suppression of schedule-controlled responding. This conclusion is supported by the similar findings in pigeons [13] and the fact that pentobarbital also often attenuates the rate-decreasing effects of anileridine [15].

The present study also extends the findings on lack of antagonism of meperidine's effects to hooded rats. It is apparent that larger doses of meperidine are required in hooded rats compared to albino rats, but there are no qualitative differences—the suppression of lever pressing by meperidine was not antagonized by naloxone in either strain of rat, whereas the analgesic effects were antagonized in both strains.

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REFERENCES

1. Campbell, O., A. H. B. Masson and W. Norris: The clinical evaluation of narcotic and sedative drugs. II: A re-evaluation of pethidine and pethilorfan. *Br. J. Anaesth.* **37:** 199–207, 1965.
2. Costa, P. J. and D. D. Bonnycastle: The effect of levallorphan tartrate, nalorphine HCl and WIN 7681 (l-allyl-4-phenyl-4-carbethoxypiperidine) on respiratory depression and analgesia induced by some active analgesics. *J. Pharmac. exp. Ther.* **113:** 310–318, 1955.
3. Downs, D. A. and J. H. Woods: Morphine, pentazocine, and naloxone effects on responding under a multiple schedule of reinforcement in rhesus monkeys and pigeons. *J. Pharmac. exp. Ther.* **196:** 298–306, 1976.
4. Dykstra, L. A., D. E. McMillan and L. S. Harris: Antagonism of morphine by long acting narcotic antagonists. *Psychopharmacologia* **39:** 151–162, 1974.
5. Foldes, F. F. and T. A. G. Torda: Comparative studies with narcotics and narcotic antagonists in man. *Acta anaesth. scand.* **9:** 121–138, 1965.
6. Gilbert, P. E. and W. R. Martin. Antagonism of the convulsant effects of heroin, *d*-propoxyphere, meperidine, normeperidine and thebaine by naloxone in mice. *J. Pharmac. exp. Ther.* **192:** 538–541, 1975.
7. Harris, L. S. and A. K. Pierson. Some narcotic antagonists in the benzomorphan series. *J. Pharmac. exp. Ther.* **143:** 141–148, 1964.
8. Harris, R. A., D. Snell, H. H. Loh and E. L. Way. Behavioral interactions between naloxone and dopamine agonists. *Eup. J. Pharmac.* **43:** 243–246, 1977.
9. Holtzman, S. G. Behavioral effects of separate and combined administration of naloxone and *d*-amphetamine. *J. Pharmac. exp. Ther.* **189:** 51–60, 1974.
10. Holtzman, S. G. Effects of morphine and narcotic antagonists on avoidance behavior of the squirrel monkey. *J. Pharmac. exp. Ther.* **196:** 145–155, 1976.
11. Holtzman, S. G. Suppression of appetitive behavior in the rat by naloxone: Lack of effect of prior morphine dependence. *Life Sci.* **24:** 219–226, 1979.
12. Janssen, P. A. J., C. J. E. Niemegeers and J. G. H. Dony. The inhibitory effect of fentanyl and other morphine-like analgesics on the warm water induced tail withdrawal reflex in rats. *Arzneimittel Forsch.* **13:** 502–507, 1963.
13. Leander, J. D. Comparing the effects of anileridine, alphaprodine, and fentanyl on schedule-controlled responding by pigeons. *J. Pharmac. exp. Ther.* **206:** 624–635, 1978.
14. Leander, J. D. An analysis of normeperidine's contribution to the rate-decreasing effects of meperidine. *Pharmac. Biochem. Behav.* **9:** 191–194, 1978.
15. Leander, J. D. Attenuating the rate-decreasing effects of phenylpiperidine analgesics by pentobarbital. *Psychopharmacology* **63:** 81–88, 1979.
16. Leander, J. D. and D. E. McMillan. Meperidine effects on schedule-controlled responding. *J. Pharmac. exp. Ther.* **201:** 434–443, 1977.
17. Lin, S.-C. C. and E. L. Way. N-dealkylation on anileridine to normeperidine. *J. Pharmac. exp. Ther.* **150:** 309–315, 1965.
18. McMillan, D. E. and J. D. Leander. Interactions between naloxone and narcotic analgesics under three schedules that induce polydipsia. *Pharmac. Biochem. Behav.* **5:** 195–200, 1976.
19. McMillan, D. E., P. S. Wolf and R. A. Carchman. Antagonism of the behavioral effects of morphine and methadone by narcotic antagonists in the pigeon. *J. Pharmac. exp. Ther.* **175:** 443–458, 1970.
20. Shannon, H. E. and S. G. Holtzman. Blockade of the discriminative effects of morphine in the rat by naltrexone and naloxone. *Psychopharmacology* **50:** 119–124, 1976.
21. Van Bever, W. F., C. J. Niemegeers, K. H. Schellekens and P. A. Janssen. N-4-substituted 1-(2-arylethyl)-4-piperidinyl-N-phenylpropanamides, a novel series of extremely potent analgesics with unusually high safety margin. *Arzheimittel-Forsch.* **26:** 1548–1551, 1976.