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Interaction of Diazepam with Meperidine or Normeperidine on Analgesia and Lethality[1]

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LEANDER, J. D. *Interaction of diazepam with meperidine or normeperidine on analgesia and lethality.* PHARMAC. BIOCHEM. BEHAV. 16(6) 1005–1007, 1982.—The effects of meperidine and normeperidine were determined alone and after pretreatment with 10 mg/kg of diazepam on the tail-withdrawal measure of analgesia in rats. Lethal doses of normeperidine were determined alone and in combination with three doses of diazepam, and lethal doses of meperidine were determined alone and in combination with 10 mg/kg of diazepam. Diazepam potentiated the analgesic effects of meperidine and increased the dose of normeperidine necessary to produce lethality.

Meperidine Normeperidine Analgesia Lethality Diazepam Rats Proconvulsive effects

MEPERIDINE is a strong analgesic like morphine which produces its analgesic effects through an interaction with a narcotic receptor [9]; however, meperidine also produces a variety of behavioral effects which do not appear to be mediated by an opiate-like activity. These effects in man include tremors, convulsions and other signs of central nervous system stimulation [3] and are most frequently observed in patients with high blood levels of the meperidine metabolite, normeperidine [13]. This laboratory has demonstrated behavioral effects of normeperidine, meperidine and several meperidine analogues which are not blocked by narcotic antagonists and do not exhibit typical narcotic cross-tolerance [6, 7, 9, 10]. These non-opioid effects on schedule-controlled responding for food by rats and pigeons by meperidine and related analogues appear functionally similar to the non-opioid, stimulatory effects in man. In pigeons, the general depressant pentobarbital attenuates the rate-decreasing effects of several of the meperidine analogues [7,8]. Likewise, diazepam effectively terminates meperidine-induced convulsions in squirrel monkeys [2]. These results have suggested the hypothesis that the effects of meperidine-like analogues are a product of two actions. One action is naloxone-sensitive and opioid in nature and is responsible for the analgesic effects [9]. The second action is not opioid-like and is related to the proconvulsive effects of these drugs [1]. The present study explores the possibility that these two actions might function in some opposition to each other. For example, the non-opioid activity might lower the analgesic effect. Meperidine and normeperidine were chosen for study because meperidine clearly exhibits both the non-opioid and opioid activities, and compared to meperidine, normeperidine has decreased opioid and increased non-opioid activities [4,12]. The present study used diazepam to decrease the proconvulsive effects of meperidine and normeperidine and this treatment potentiated the analgesic effects of meperidine while decreasing the lethal effects of normeperidine.

METHOD

Animals

Male-Sprague-Dawley-derived albino rats were used (a pool of 24 were used in analgesia testing and 70 were used in lethality testing). All were more than six months old, varied in body weight from 350 to 510 grams and were distributed across all experimental groups. Food and water were available freely in the home cages, except that food was removed from the cages 12 hours before the animals were used in the experiments.

Analgesia Testing

The test used for measurement of an analgesic effect was the tail-withdrawal reflex induced by application of warm water to the tail [6]. The animal was orally intubated with either 10 mg/kg of diazepam or diazepam vehicle and placed in a standard rat holder with the tail hanging free outside the holder. The rat remained in the holder for the next two hours. Thirty minutes after being placed in the holder, the rat was injected intraperitoneally with varying doses of meperidine or normeperidine.

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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 rat did not remove his tail from the water with 15 sec, the tail was removed from the water by the experimenter and the latency was assigned a value of 15 sec (15 sec cut-off time). These latency measures were made at 15 min before and 15, 30, 60 and 90 min after injection of either meperidine or normeperidine in order to determine the time- and dose-effects of the drug treatments. During the course of the analgesia testing, the rats were used repeatedly (though not all rats received all treatments), with each rat receiving a different order of dose administration. The effects of meperidine were determined before the effects of normeperidine. Generally each of the dose combinations was given to 2 rats on each test day. These procedures were replicated until each dose combination had an n=6 (except n=4 for 10 diazepam + water combination). Drugs were administered no more frequently than twice a week with at least two drug-free days between test days. There was no evidence that twice-weekly administration of the short-acting narcotic, meperidine, produced any tolerance development.

The meperidine and normeperidine doses were calculated as the hydrochloride salts and were administered in a volume of 1 ml/kg of body weight. The diazepam dose was calculated as the base and administered in a volume of 2 ml/kg of body weight. The vehicle for the diazepam was the commercially available vehicle (40 percent propylene glycol, 10 percent ethanol, 5 percent sodium benzoate and benzoic acid as buffers and 1.5 percent benzyl alcohol as preservative).

Lethality Determination

For the lethality testing the rats were orally intubated with diazepam vehicle in a volume of 4 ml/kg or various doses of diazepam 30 minutes before receiving intraperitoneally either a dose of meperidine or normeperidine. The meperidine and normeperidine were dissolved in distilled water in a volume of 40 mg/ml. The volume injected was varied to arrive at the desired dose.

RESULTS

Figure 1 shows the effects of various doses of meperidine and normeperidine in the tail-withdrawal procedure at the various time periods during which the rat was in the holder. The control latency averaged around 5 to 6 seconds in these rats. The top left frame shows that the 10 mg/kg dose of diazepam, followed a half-hour later by an intraperitoneal dose of distilled water, had no effect on the tail-withdrawal latency throughout the two-hour period in which the rat was in the holder. As the dose of meperidine was increased from 5 to 10 and 20 mg/kg, there was a dose-related increase in the latency within 15 to and 30 minutes after meperidine alone. the 10 mg/kg dose of diazepam had no effect in combination with 5 mg/kg of meperidine, but enhanced the analgesic effect of 10 ($p<0.05$ at +15 and +60 min) and 20 ($p<0.05$ or less at +15, +30, +60 and +90 min) mg/kg of meperidine.

Normeperidine had only a slight effect on tail-withdrawal latency, with the 40 mg/kg dose increasing the 30-minute tail withdrawal to 8.53 seconds. Diazepam did not have a consistent effect in combination with normeperidine on the analgesic measure. The main effect of 40 mg/kg of normeperidine alone was less than that of the combination, but there was some overlap between the groups because of large variability

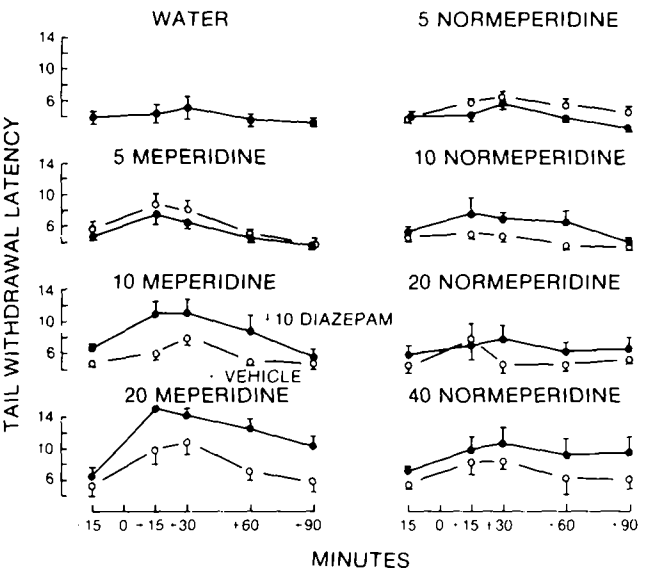

FIG. 1. Meperidine- and normeperidine-induced analgesia measured using tail-withdrawal latency. Ordinates are latency (in sec) to withdraw tail from 55°C hot water. Abscissae are time (in min) before (-) or after (+) the injection (which occurred at 0 time) of meperidine or normeperidine. Each point (and bracket) is the mean (±SEM) of 6 rats (except for the 10 diazepam plus water combination, which was n=4). Open circles show the effects of meperidine or normeperidine administered after pretreatment with the diazepam vehicle. Filled circles show the effects when 10 mg/kg of diazepam was the pretreatment.

within each treatment condition. For example, within the diazepam pretreatment plus 40 mg/kg of normeperidine treatment, there were two rats that failed to withdraw their tails within the 15 sec cut-off period for at least four different time periods, whereas a third rat had a consistently short latency ranging from 1 to 3.8 sec after the normeperidine injection.

The effects of various meperidine and normeperidine doses in combination with doses of diazepam on lethality are shown in Table 1. The combination of 80 mg/kg of normeperidine plus diazepam vehicle killed all five rats to which it was given. Diazepam produced a dose-related antagonism of normeperidine's lethal effects with 120 mg/kg of normeperidine required to kill rats pretreated with 20 mg/kg of diazepam. Though the 10 mg/kg dose of diazepam did appear to provide some protection against meperidine's lethal effects, diazepam's protection was not as effective as it was against normeperidine.

DISCUSSION

The present study shows that diazepam potentiates the analgesic effects (increased tail-withdrawal latency) of meperidine probably by reducing the proconvulsive effects of this drug [1]. An analgesic effect of normeperidine has previously been reported in the literature for mice [13] and rats [2], though it was not clearly seen in this study. An analgesic effect of normeperidine is often difficult to demonstrate since normeperidine is a third less potent than meperidine as an analgesic but is considered twice as potent as meperidine as a convulsant [13].

TABLE 1

EFFECTS OF DIAZEPAM ON THE LETHAL EFFECTS OF NORMEPERIDINE AND MEPERIDINE (NUMBER OF RATS WHICH DIED/NUMBER INJECTED WITH THE COMBINATION)

	Diazepam Doses			
	0 mg/kg	5 mg/kg	10 mg/kg	20 mg/kg
60 mg/kg Normeperidine	0/5			
80 mg/kg Normeperidine	5/5	1/5	0/5	
100 mg/kg Normeperidine		4/5	1/5	0/5
120 mg/kg Normeperidine			4/5	5/5
80 mg/kg Meperidine	4/5		3/5	
100 mg/kg Meperidine	5/5		2/5	
120 mg/kg Meperidine			4/5	

These data complement those reviewed in the introduction which indicate that meperidine and related anlogues have two actions, one opioid and another related to the proconvulsive actions of these compounds. With the higher doses, these proconvulsive actions produce convulsions and death (as in the present study), whereas at lower doses these proconvulsive actions suppress schedule-controlled behavior [7, 8, 10, 11] and lower seizure thresholds [1].

The proconvulsive (non-opioid) and opioid actions of these compounds appear to be somewhat antagonistic in function. The evidence for that is that diazepam potentiated the opioid action (analgesia) in the present study, whereas blocking the opioid effects with the narcotic antagonist, naloxone, potentiates the proconvulsive (non-opioid) actions of these drugs [1, 7, 11, 12].

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