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Meperidine does not Block the Cholinergic Effects of Oxotremorine

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LEANDER, J. D. *Meperidine does not block the cholinergic effects of oxotremorine.* PHARMAC. BIOCHEM BEHAV. 10(6) 941–942, 1979.—Meperidine (20 and 40 mg/kg, IP) did not block the cholinergic effects (tremor, salivation, and tearing) produced by oxotremorine (0.4 mg/kg, SC) in rats, whereas atropine blocked these three effects (10 mg/kg, 2.5 mg/kg and 0.08 mg/kg, respectively).

Meperidine Anticholinergic Rats Oxotremorine

THE effects of meperidine in laboratory animals have frequently been shown to differ qualitatively from those of other narcotic agonists. For example, operant responding maintained by food presentation to food-deprived rats or pigeons can be suppressed by high doses (10–30 mg/kg) of meperidine and morphine, however, meperidine's behavior suppressing effects cannot be antagonized by narcotic antagonists whereas those effects of morphine can be antagonized [6,7]. Likewise, the behavior suppressing doses of morphine show evidence for tolerance in methadone-maintained animals whereas there is no evidence for methadone-induced cross tolerance to the behavior suppressing doses of meperidine [6].

A possible mechanism for these qualitative differences between morphine and meperidine arises from a fairly common belief that meperidine has anticholinergic (antimuscarinic) effects. This belief apparently arises from several sources (as reviewed by Eddy *et al.* [1]): (1) meperidine was synthesized in a series of atropine-like compounds: (2) meperidine has been reported to have spasmolytic effects on smooth muscle; (3) and meperidine has been reported to produce dryness of mouth as a side effect. However, the review by Eddy *et al.* [1] also notes numerous inconsistencies with this anticholinergic hypothesis. For example, meperidine has also frequently been reported to produce spasmogenic effects on smooth muscle. The present study was conducted to determine if any evidence for direct anticholinergic effects of meperidine could be found for doses (20 and 40 mg/kg, IP) of meperidine which completely eliminate schedule-controlled responding in rats, and which cannot be antagonized by narcotic antagonists [7].

Oxotremorine is a direct-acting cholinergic agonist and produces a variety of cholinergic responses when injected into rodents. Blockade of these responses has been used to show direct anticholinergic effects of diverse drugs and this in vivo effect correlates with in vitro measures of cholinergic receptor blockade [2, 3, 4, 9]. Oxotremorine's effects can be divided into centrally mediated (tremor) and peripherally mediated (salivation and tearing), and thus the anticholinergic effects can be evaluated for both peripheral and central blockade of muscarinic receptors [5]. For example, atropine methyl nitrate blocks the salivation and tearing, but not the tremors produced by oxotremorine [12].

METHOD

In the present study, either of 2 doses (20 and 40 mg/kg, IP) of meperidine HCl (Sterling-Winthrop Research Institute), 8 doses (0.08–20 mg/kg, IP) of atropine sulfate, or water was administered 20 minutes before a 0.4 mg/kg, SC injection of oxotremorine (Aldrich). In this laboratory, the 20 and 40 mg/kg doses of meperidine completely eliminate schedule-controlled responding of rats ([7] and unpublished studies), and this effect is not antagonized by naloxone. All drugs were dissolved in distilled water and given in a volume of 1 ml/kg. The rats were observed at 10, 20 and 40 minutes after oxotremorine and scored for the presence or absence of tremors, salivation, or tearing. No attempt was made to grade the severity of the tremor or the amount of salivation or tearing. The person doing the scoring was blind to the pretreatment conditions. The rats were Sprague-Dawley females obtained from Charles River, weighing between 250–310 g and were food and water deprived after the pretreatment injection. Animals were housed singly in standard wire mesh cages throughout the entire experiment. The experiments were conducted between 9:00 a.m. and 12 noon. The rats were used in several dose-combinations, but never more frequently than every fifth day.

RESULTS AND DISCUSSION

Table 1 shows the results. The 10 mg/kg dose of atropine blocked both the central and peripheral cholinergic effects of oxotremorine, whereas smaller doses of atropine only blocked the peripheral effects (salivation and tearing). Even doses as low as 0.16 and 0.08 mg/kg of atropine block the tearing produced by oxotremorine. In contrast with the effects seen with the prototype anticholinergic agent, atropine, there was no clear evidence that meperidine blocked the

TABLE 1

PRESENCE OF EFFECT/NUMBER OF RATS TESTED

	Tremors	Salivation	Tearing
Control	4/4	4/4	4/4
40 mg/kg Meperidine HCl	5/7	7/7	7/7
20 mg/kg Meperidine HCl	7/8	8/8	7/8
20 mg/kg Atropine Sulfate	0/4	0/4	0/4
10 mg/kg Atropine Sulfate	0/4	0/4	0/4
5 mg/kg Atropine Sulfate	1/4	0/4	0/4
2 5 mg/kg Atropine Sulfate	3/4	0/4	0/4
1 28 mg/kg Atropine Sulfate	4/4	2/4	0/4
0.64 mg/kg Atropine Sulfate	4/4	2/4	0/4
0.16 mg/kg Atropine Sulfate	4/4	4/4	1/4
0 08 mg/kg Atropine Sulfate	4/4	4/4	0/4

effects of oxotremorine. Two animals did not exhibit tremor after the 40 mg/kg dose of meperidine, but this is probably due to the fact that 40 mg/kg meperidine produces some muscle rigidity. One of 8 animals injected with 40 mg/kg of meperidine died before the oxotremorine was injected, so higher doses of meperidine were not tested.

The present results suggest that meperidine has no direct anticholinergic effects, either centrally or peripherally, as measured by the inability to block the cholinergic effects of oxotremorine. This conclusion is compatible with earlier results showing that meperidine was ineffective in blocking acetylcholine-induced fall in blood pressure in dogs [8] and that meperidine produced effects opposite to those of atropine on small intestine motility and heart rate [11]. Thus, the long-held belief that meperidine produces its qualitative behavioral differences from morphine and other narcotic agonists through a direct anticholinergic action should be abandoned.

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