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An Analysis of Normeperidine's Contribution to the Rate-Decreasing Effects of Meperidine[1]

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LEANDER, J. D. *An analysis of normeperidine's contribution to the rate-decreasing effects of meperidine.* PHARMAC. BIOCHEM. BEHAV. 9(2) 191–194, 1978.—The effects of normeperidine (1–17.5 mg/kg) alone and in the presence of naloxone (1 and 10 mg/kg) were studied in pigeons responding under a multiple fixed-ratio 30 response, fixed-interval 5-min schedule of food presentation. Naloxone only potentiated the rate-decreasing effects of normeperidine. The effects of meperidine also were studied after pretreatment with SKF-525A (25 and 50 mg/kg), an inhibitor of drug metabolism. SKF-525A had no effects on responding when administered alone, but it potentiated the rate-decreasing effects of meperidine. It was concluded that meperidine's rate-decreasing effects cannot be due to normeperidine, the metabolite, but rather that both of these drugs have non-narcotic actions which produce decreases in schedule-controlled responding.

Normeperidine Meperidine SKF-525A Schedule-controlled responding

MEPERIDINE, a synthetic narcotic, is as effective as morphine in relieving pain in man [11], but differs from morphine by producing tremors, incoordination, and convulsions at high doses [1, 18, 19, 26]. In addition these effects of high doses in man and animals are not antagonized by narcotic antagonists (naloxone and nalorphine), whereas the effects of high doses of morphine or heroin are antagonized [13, 19, 24, 27].

This laboratory has reported recently on the effects of meperidine on the schedule-controlled responding of pigeons [21] and rats [22]. In these studies, naloxone and cyclazocine failed to antagonize the rate-decreasing effects of meperidine. It was suggested [21] that the rate-decreasing effects of meperidine might be due to formation of the metabolite, normeperidine [3, 24, 25]. Normeperidine is a convulsant agent void of any narcotic-like effects [8,13] and not antagonized appreciably by naloxone [13] or nalorphine [24].

The present experiments were conducted to determine whether the effects of meperidine could be attributed to normeperidine. First the effects of normeperidine were studied alone and in the presence of two doses of naloxone. This was done in order to determine the potency of normeperidine as compared to meperidine as previously reported [21] and to see if the behavioral effects of normeperidine could be antagonized by naloxone. Secondly, the behavioral effects of meperidine were studied after pretreatment with SKF-525A, an inhibitor of drug metabolism. SKF-525A has been reported to potentiate the analgesic effects of meperidine [6], apparently by decreasing the rate of metabolism of meperidine to normeperidine since a 40 min pretreatment of 50 mg/kg of SKF-525A doubles the body level of meperidine and decreases the level of normeperidine by 80% 1 hr after injection of meperidine [2]. In fact, Deneau and Nakai [8] have reported that SKF-525A changed the pattern of meperidine-induced toxicity in the rhesus monkey from one of convulsions and tremors to one of sedation and respiratory depression. They attributed this change in the pattern of toxicity to the decrease in the metabolism of meperidine to normeperidine. Though inhibition of meperidine metabolism by SKF-525A has not been shown in birds, inhibition of the metabolism of pentobarbital and morphine by SKF-525A appears to be similar in birds and mammals [16].

METHOD

Animals

The animals used were six male white Carneaux pigeons maintained at 80% (420–470 g) of their free-feeding weights by restriction of their post-session feedings. Water, however, was available freely in the test and home cages. All birds (except #947) had extensive histories with the multiple fixed-ratio fixed-interval schedule and with narcotics, narcotic antagonists, antipsychotic drugs and pentobarbital before this experiment began. There is no evidence that this previous history has any determining effects on the present results.

Apparatus

The experimental chambers, patterned after those of Ferster and Skinner [12], were sound attenuating and ventilated. The experimental space was approximately 29 cm high

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by 27 cm wide by 29 cm long. A translucent response key, 2 cm dia., was mounted 22 cm above the wire mesh floor. The response key could be transilluminated by red or blue lights. Opening of the key contacts with a minimum force of 0.15 Newtons defined the key-peck response and produced an audible click from a feedback relay. Grain could be presented through a rectangular opening below the response key and 6 cm above the floor. A 7.5 W bulb illuminated the chamber, except during the 4-sec grain presentation cycle, during which all lights were extinguished except one illuminating the grain. Electromechanical programming and recording equipment were housed in an adjacent room.

Procedure

The schedule of food presentation, a multiple fixed-ratio 30 response, fixed-interval 5-min schedule limited hold 40 sec [12], is described as follows. When the fixed ratio 30 (FR 30) was in effect, a blue light transilluminated the response key, and the 30th key peck resulted in 4-sec access to grain. When the fixed-interval 5-min (FI 5) schedule was in effect, the first response after 5 min had elapsed in the presence of a red transilluminated response key resulted in grain presentation. Schedule components alternated after each grain presentation. If the animal allowed 40 sec to elapse in the FR 30 component without completing the ratio requirement, the schedule in effect switched to the FI 5 component. If 40 sec elapsed without a response after the FI 5 min elapsed, the schedule in effect switched to the FR 30 component. Experimental sessions were terminated by the first schedule-component switch after an hour. Animals were tested Monday through Friday, with Tuesdays and Fridays usually serving as drug injection days, and Thursdays serving as water injection days.

Drugs

The drugs used and the forms in which the doses were calculated are meperidine hydrochloride and normeperidine hydrochloride (donated by Sterling-Winthrop Research Institute, Rensselaer, NY), naloxone hydrochloride (donated by Endo Laboratories, Inc., Garden City, NY), and SKF-525A (β-dimethylaminoethyl-2,2-diphenylpropylacetate hydrochloride) (donated by Smith, Kline, and French Laboratories, Philadelphia, PA). All drugs were dissolved in distilled water which was used also for control injections. All injections were administered in the breast muscle in a volume of 1 ml per kg of body weight. When the interaction of normeperidine and naloxone were studied, injections of each drug were given within 15 sec of each other in no systematic order in opposite sides of the breast muscle, 10 min before the test sessions began. When the effects of SKF-525A were studied with meperidine, the SKF-525A was administered 40 min before the administration of meperidine which was 10

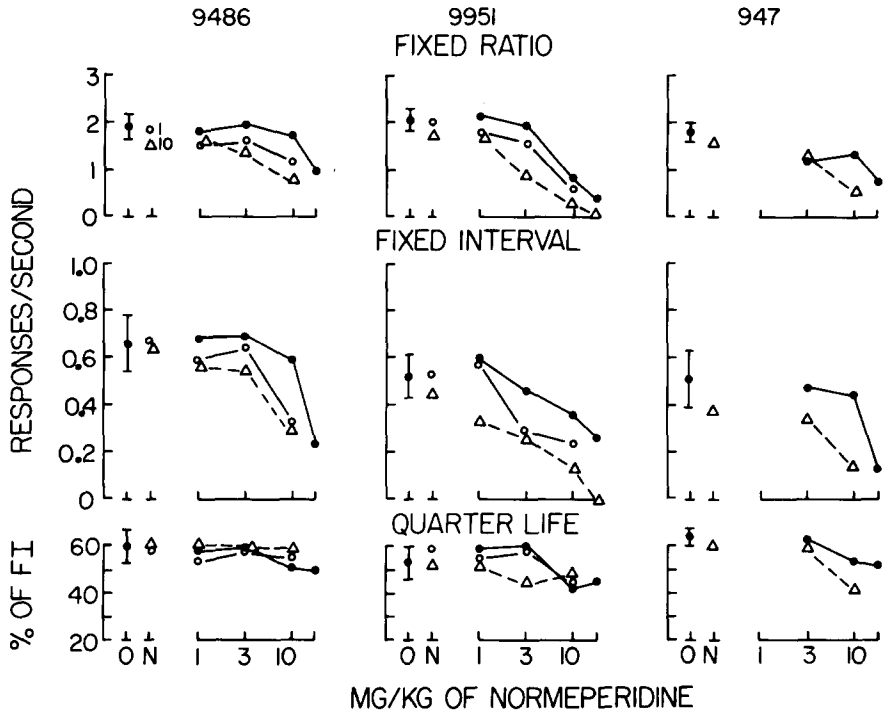

FIG. 1. Effects of normeperidine alone (●) and in combination with 1 (○) or 10 (△) mg/kg of naloxone on rates of responding within the fixed-ratio component (top row) and fixed-interval component (middle row) and on the fixed-interval quarter-life value (bottom row) for three pigeons (9486, 9951, and 947). Abscissa: dose of normeperidine, log scale; Ordinate: rates of responding as responses per sec, and quarter-life value as % of fixed interval. The points (and brackets) at 0 are the means (± SD) for more than 40 water injection control sessions. Points above N are the effects of 1 mg/kg (○) and 10 mg/kg (△) of naloxone alone. Each drug point is at least the mean of two determinations. Doses of naloxone and normeperidine were given virtually simultaneously.

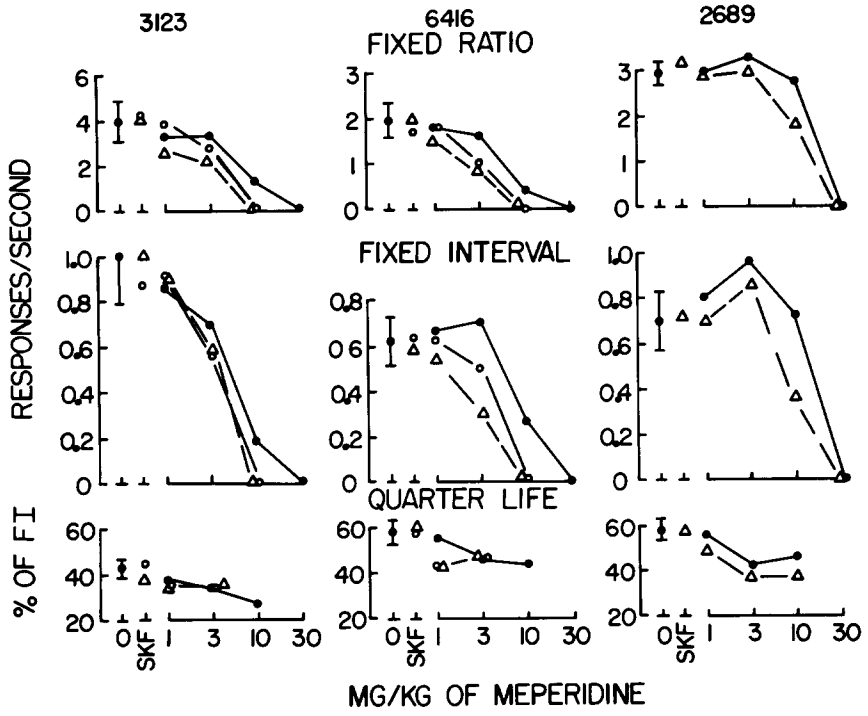

FIG. 2. Effects of meperidine alone (●) and after pretreatment (40 min) with 25 (○) or 50 (△) mg/kg of SKF-525A on the rates of responding within the fixed-ratio component (top row) and fixed-interval component (middle row) and on the fixed-interval quarter-life value (bottom row) for three pigeons (3123, 6416, and 2689). Abscissa: dose of meperidine, log scale. The points (and brackets) at 0 are the mean (± SD) of 16–18 water injection control sessions. Points above SKF are the effects of pretreatment with 25 mg/kg (○) and 50 mg/kg (△) alone 40 min before testing. Each drug point is the mean of two or three determinations.

min before the test session began. This pretreatment time has been shown to be optimal for inhibition of drug metabolism and potentiation of narcotics, barbiturates and other drugs [2, 5, 6, 7].

Measurement of Drug Effects

Average rates of responding for each bird during the FR and FI components were calculated from digital counters and elapsed-time meters. The quarter-life value of the FI was calculated by linear interpolation from counters recording the distribution of responding within the FI. The quarter life is a statistic independent of response rate used to describe quantitatively the positively accelerated pattern of responding within the FI. The quarter-life value is defined as the percentage of the FI taken for the bird to emit 25% of the total responses in the FI [15,17].

RESULTS AND DISCUSSION

Figure 1 shows the effects of normeperidine on the schedule-controlled responding of three pigeons. Generally, normeperidine decreased responding under both schedule components only at the higher doses (10 and 17.5 mg/kg) and lower doses had little effect. The only exception is bird 947, in which even the 3 mg/kg dose of normeperidine alone decreased the rate of responding within the FR component.

The effects of naloxone administered alone were negligible, except for a slight tendency to decrease responding with the 10 mg/kg dose. When combined with normeperidine, naloxone potentiated the rate-decreasing effects of normeperidine ($p<0.01$, Sign test). This potentiation of the rate-decreasing effects of normeperidine, rather than antagonism, is similar to the effects seen with the parent compound, meperidine in rats [22] and pigeons [21], and contrasts with the antagonisms of morphine, methadone, and etonitazene by naloxone [9, 10, 14, 23].

Figure 2 shows the effects of meperidine alone and after pretreatment with two doses of SKF-525A in 3 pigeons. Without any pretreatment, meperidine decreased rates of responding at 10 and/or 30 mg/kg in all birds and increased responding in the FI in one bird (2689) at 3 mg/kg. These effects of meperidine are similar to those previously reported [21]. Pretreatment with 25 or 50 mg/kg of SKF-525A had no effects when administered alone. However, these doses of SKF-525A when given before meperidine produced potentiation of meperidine's rate-decreasing effects ($p<0.01$, Sign test). Good examples of this potentiation occurred with the 3 mg/kg dose of meperidine in bird 6416 and the 10 mg/kg dose in bird 2689. In these birds, these doses of meperidine were ineffective in decreasing responding, whereas when given after pretreatment with SKF-525A they reduced responding to approximately 50% of control levels.

Since SKF-525A has been shown to inhibit the metabolism of meperidine [2], it can be inferred that this potentiation of meperidine's effects are due to inhibition of the metabolism of meperidine resulting in more active drug in the body and that the metabolism of meperidine leads to

metabolites which are less active than the parent drug. Thus one cannot conclude that meperidine's effects are primarily a result of the actions of normeperidine although, as shown in Fig. 1, normeperidine is approximately equal in potency in decreasing responding to meperidine and shows the same lack of antagonism by naloxone as does meperidine. A revised hypothesis would suggest that meperidine and normeperidine produce their rate-decreasing effects via a common mechanism which is unrelated to any interaction with narcotic receptors, since naloxone did not antagonize the effects. Because normeperidine appears devoid of narcotic action, it can be considered the best agent for further study of this non-narcotic action of meperidine and related drugs.

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