

Attenuation of the Behavioral Effects of Meperidine and Normeperidine by Daily Administration of Diazepam¹

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Received 14 May 1982

LEANDER, J. D. *Attenuation of the behavioral effects of meperidine and normeperidine by daily administration of diazepam.* PHARMACOL BIOCHEM BEHAV 18(1) 95-101, 1983.—The effects of meperidine, normeperidine, morphine, pentobarbital and *d*-methadone were determined on the key-pecking behavior of pigeons responding under a multiple fixed-ratio (FR), fixed-interval (FI) schedule of grain presentation. Dose-effect curves were obtained for each drug alone and during daily administration of 10 mg/kg of diazepam. The daily administration of diazepam had little effect on the behavior itself. Meperidine and normeperidine caused dose-related decreases in both FI and FR responding. The dose-effect curves for these drugs during daily administration of diazepam were shifted to the right compared to the dose-effect curves determined in the absence of daily diazepam. In contrast, the effects of morphine, *d*-methadone and pentobarbital either were not affected by daily administration of diazepam or were shifted to the left by daily administration of diazepam. These data further support the hypothesis that the behavioral effects of meperidine and normeperidine are due to a proconvulsive action produced by these drugs. In contrast, the effects of morphine, *d*-methadone and pentobarbital are not due to such a proconvulsive action.

Meperidine Normeperidine Diazepam Schedule-controlled behavior

MEPERIDINE is a strong analgesic agent as effective as morphine in man [17]. The analgesic effects of meperidine are produced through an interaction with an opioid receptor which is antagonized by naloxone [23]; however, other effects are produced which are not a result of an interaction at an opioid receptor. Unlike morphine, high doses of meperidine often produce tremors, incoordination, convulsions and even psychotic-like symptoms in man [1, 13, 15]. Upon chronic administration of meperidine, tolerance develops to the analgesic effects but not to the toxic effects of high doses [13,15]. In laboratory animals, the toxic effects of meperidine are not as well antagonized by the narcotic antagonists, naloxone and nalorphine, as are the toxic effects of morphine or heroin [7, 14, 34, 35]. In fact, naloxone has been reported to potentiate the proconvulsive effects of meperidine in the rat [4].

Recently, in studies of the effects of meperidine on the schedule-controlled behavior of rats and pigeons, naloxone and cyclazocine did not antagonize the rate-decreasing effects of high doses of meperidine, whereas the effects of other opioids such as morphine, methadone and etonitazene were readily antagonized [5, 29, 31, 32]. Likewise, daily administration of methadone produced a 10-fold shift of morphine's dose-effect curve but no shift in meperidine's dose-effect curve for responding in the pigeon [29]. Since the

behavioral effects of meperidine on schedule-controlled responding were not antagonized by naloxone and did not show opioid-induced cross tolerance, they are referred to in this paper as non-opioid in nature. Similar non-opioid effects were exhibited by the *n*-demethyl metabolite of meperidine, normeperidine [19], and the meperidine analogs, anileridine, alphaprodine, ethoheptazine and azabicyclane [18,21].

Though these non-opioid effects of the meperidine analogs are not antagonized by naloxone, they are attenuated by intermediate doses of pentobarbital [20,21]. Acute doses of diazepam will also attenuate the non-opioid behavioral suppressing effects of meperidine and normeperidine, though not to the same extent as pentobarbital [20,27]. This apparently less effective attenuation by acute doses of diazepam may be due to the rate-decreasing effects of acute administration of diazepam since attenuation only occurs at doses that suppress schedule-controlled responding in the pigeon when given alone. The purpose of the present study was to study the effects of daily administration of diazepam on the dose-effect curves of meperidine, normeperidine and morphine in order to determine if daily administration of diazepam would attenuate the behavioral effects of meperidine and normeperidine. Daily administration of diazepam was used since others have shown that tolerance occurs to the sedative effects of benzodiazepines

¹This work was supported by U.S.P.H.S. Grant DA-01711.

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[8,30]. It was reasoned that if tolerance occurred to the rate-decreasing effects of diazepam, attenuation of the rate-decreasing effects of meperidine and normeperidine might be better exhibited. The second purpose of the present study was to determine the effects of daily administration of diazepam on the dose-effect curve for pentobarbital and *d*-methadone. *d*-Methadone has the similarity to meperidine and normeperidine of being an opioid agent which produces behavioral effects which are not antagonized by opioid antagonists and do not show opioid-induced cross tolerance [28]. If the shift of meperidine's and normeperidine's dose-effect curves was due to nonspecific mechanisms such as increased rate of metabolism as a result of the chronic diazepam treatment, a similar shift for pentobarbital and *d*-methadone might be expected. The present study shows that daily administration of diazepam produced a shift to the right of the dose-effect curves for meperidine and normeperidine, whereas the dose-effect curves for pentobarbital, *d*-methadone and morphine were either unaffected or shifted to the left.

METHOD

Animals

Male, White Carneaux pigeons from the Palmetto Pigeon Plant (Sumter, SC) were housed in individual wire mesh cages and maintained at approximately 80 percent of their free-feeding weight by pigeon grain presented during the experimental sessions and by post-session supplemental feedings. Water and oyster shell grit were always present in the home cage and water was also available in the test chamber. All birds had extensive and varied histories of responding under schedules of grain presentation and also with injections of diverse psychoactive drugs prior to the beginning of the present study.

Apparatus

The test chamber was sound attenuating and ventilated [6]. The space for the bird measured 29 cm high \times 27 cm wide \times 29 cm long. A translucent key could be transilluminated by red or blue lights. A key peck with a minimal force of 0.15 N operated the key and defined the response. Below this response key was an opening through which the pigeon could be given access to pigeon grain. The experimental space was illuminated by a 7.5 W bulb. During the 4-second grain presentation cycle, all lights in the chamber were extinguished except one illuminating the presented grain. Programming and recording equipment were housed in an adjacent room and recorded all the data.

Procedure

The multiple FR 30-response, FI 5-minute schedule (mult FR-30, FI-5) can be described in the following manner [6]. When a blue light transilluminated the response key, the 30th response produced the 4-second access to grain (FR-30). When a red light transilluminated the response key, the first response to occur after 5 minutes elapsed produced access to grain. The bird had 40 seconds to emit the 30 responses in the FR component and up to 40 seconds after the 5 minutes had elapsed to respond in the FI component and produce grain presentation (limited hold=40 sec). The FI and FR components alternated after each grain presentation or when the limited hold elapsed. Test sessions were conducted Monday through Friday for one hour each day and began in the FR component.

Administration of Drugs

The drugs used and the forms in which the doses were calculated were meperidine-HCl and normeperidine-HCl (gift from Sterlint Winthrop Research Institute, Rensselaer, NY), *d*-methadone-HCl (gift from Eli Lilly and Company, Indianapolis, IN), diazepam (gift from Hoffman-LaRoche, Nutley, NJ), morphine sulfate and pentobarbital sodium. All drugs except diazepam were dissolved in distilled water, and distilled water was used for control injections for those drugs. All injections except diazepam were administered in a volume of 1 ml/kg of body weight into the breast muscle 10 minutes before the test sessions began. These injections occurred no more frequently than twice a week (usually on Tuesdays and Fridays). Injections of distilled water were administered on Thursdays, and the data obtained on Thursdays served as non-drug control data against which to evaluate the drug data. During the chronic administration of diazepam, diazepam was suspended in a 5 percent acacia solution and was administered in a volume of 2 ml/kg by passing a 15-cm feeding needle down the throat of the bird through the crop to the proventriculus. This dosing of diazepam occurred 60 minutes before the test sessions began on weekdays and also occurred on the weekends.

Measurement of Drug Effects

Average rates of responding for each individual bird during the FR-30 and FI-5-minute components were computed in responses/second from digital counters and elapsed time meters. Drug effects were then calculated as a percentage of each animal's mean control value obtained on sessions during which injections of distilled water occurred. The distribution of responses within the FI component of the multiple schedule was obtained by dividing the interval into ten 30-second segments and recording the number of responses in each segment. These data were used to calculate the quarter-life value, a statistic which is independent of response rate and is used to describe quantitatively the positively accelerated pattern of responding that occurs under the FI schedule. The quarter-life value is the percentage of the FI required for the bird to emit 25 percent of the total responses in the fixed interval [10,12]. The data from the tenths of the FI were also used to determine the effects of the drugs on the local rates of responding [26].

RESULTS

Control Performances

Table 1 shows the mean data from control sessions for each bird. The control performances under the multiple FR, FI schedules were similar to those previously reported for pigeons under similar test conditions [18, 19, 26]. In the FR component of the multiple schedule there was a brief post-reinforcement pause followed by an abrupt transition to a high rate of responding that continued until 30 responses were completed and grain was presented. The mean rates of responding varied from 2.11 to 3.24 responses/second for individual birds under the FR schedule. At the start of each FI component, there was little or no responding which was then followed by a positively accelerated pattern of responding toward the end of the FI. The mean rate of responding ranged from 0.5 responses/second to 1.2 responses/second in individual birds. The quarter-life value, an indication of the positively accelerated pattern of responding, ranged from 55-60 percent of the fixed interval.

TABLE 1

MEAN VALUES \pm S.D. OF RESPONSE RATES (RESPONSES/SECOND) IN THE FIXED-RATIO AND FIXED-INTERVAL COMPONENTS OF THE MULTIPLE SCHEDULE AND THE FIXED-INTERVAL QUARTER-LIFE VALUE (AS A PERCENT OF THE FIXED-INTERVAL REQUIRED FOR EMISSION OF 25 PERCENT OF THE TOTAL RESPONSES) FOR INDIVIDUAL PIGEONS BASED ON CONTROL IM INJECTION SESSIONS IN THE ABSENCE OF DAILY DIAZEPAM PRETREATMENT

Subject	Fixed-ratio rates	Fixed-interval rates	Fixed-interval Quarter-life	Number of Sessions
3940	2.47 \pm 0.24 (3.06 \pm 0.26)	0.60 \pm 0.08 (0.74 \pm 0.11)	59 \pm 3 (48 \pm 5)	13 (11)
2248	3.24 \pm 0.23 (3.04 \pm 0.60)	1.23 \pm 0.25 (1.64 \pm 0.26)	56 \pm 5 (47 \pm 7)	10 (12)
4632	2.46 \pm 0.07 (2.56 \pm 0.06)	1.05 \pm 0.12 (0.92 \pm 0.15)	55 \pm 4 (54 \pm 4)	11 (8)
1604	2.70 \pm 0.17 (2.48 \pm 0.24)	0.93 \pm 0.10 (0.84 \pm 0.36)	58 \pm 3 (59 \pm 11)	10 (4)
2428	2.63 \pm 0.24 (3.10 \pm 0.24)	0.51 \pm 0.09 (0.46 \pm 0.02)	60 \pm 5 (46 \pm 6)	5 (4)
1104	3.10 \pm 0.15 (2.80 \pm 0.15)	0.88 \pm 0.08 (0.91 \pm 0.09)	56 \pm 2 (56 \pm 5)	5 (4)
4513	2.11 \pm 0.21 (2.19 \pm 0.16)	0.52 \pm 0.08 (0.50 \pm 0.14)	59 \pm 4 (49 \pm 8)	6 (3)

Values during daily diazepam are shown in parentheses.

Comparisons of Morphine, Meperidine and Normeperidine

Figure 1 shows the effects of morphine, meperidine and normeperidine in three birds and the effects of meperidine and normeperidine in a fourth bird. Without the pretreatment of diazepam, morphine, meperidine and normeperidine produced dose-related decreases in responding under both schedules of grain presentation in all birds. The dose which decreased responding to a near zero level varied between birds, however. In birds 2248 and 3940, 10 mg/kg of morphine and meperidine produced near complete cessation of responding throughout the entire session, and a dose of 17.5 mg/kg of normeperidine produced a similar effect. In bird 4632, 30 mg/kg of morphine produced about a 50 percent suppression of responding and 17.5 mg/kg of meperidine was required to suppress responding. Likewise, in bird 4632 a dose of 30 mg/kg of normeperidine was required to suppress responding to a near zero level. In bird 1604, 30 mg/kg of both meperidine and normeperidine was required prior to treatment with diazepam to produce a near zero level of responding.

Acute administration of 10 mg/kg of diazepam decreased rates of responding in both schedule components in all birds, but tolerance developed to this effect within 3 to 5 days. The effect of daily administration of 10 mg/kg of diazepam varied across the four birds. For example, in bird 2248 the daily administration of diazepam had no effect on FR responding, but produced a slight increase in FI responding. In bird 3940, daily diazepam produced a slight increase in FR responding, with less of an effect on FI responding. In birds 4632 and 1604, daily administration of diazepam had no effect on either FI or FR responding. The effects of daily diazepam treatment, however, did have a reliable effect on the dose-

effect curves of meperidine and normeperidine in all four birds. Both the meperidine and normeperidine dose-effect curves for rates of responding in both FI and FR schedules in all four birds were shifted to the right by daily administration of diazepam, whereas the effects of meperidine and normeperidine on the quarter-life value were enhanced by daily diazepam. In contrast to the effects of meperidine and normeperidine, the dose-effect curves for morphine on rates of responding were either not affected by the daily administration of diazepam or were shifted to the left. This shift to the left of morphine's rate-decreasing effect was most noticeable in the FI component for bird 3940 and in both the FI and FR components for bird 4632. Likewise, the daily administration of diazepam enhanced the decrease in quarter-life value produced by increasing doses of morphine.

Figure 2 shows the effects of two doses of morphine and two doses of meperidine in two birds (bird 2248 and bird 3940) on the local rates of responding within the FI component and the FR component. The drug rates were plotted as a function of the rates of responding after water injection. In bird 2248 the effect of 3 mg/kg of morphine did not differ between before and during diazepam treatment. The rate-decreasing effect of 10 mg/kg of morphine, however, was enhanced by daily diazepam treatment. As can be seen in the figure, local rates of responding after morphine were more suppressed under the condition of daily diazepam treatment than they were without diazepam treatment. Likewise, for bird 3940 with both 1 and 3 mg/kg of morphine, similar local rates of responding were decreased more during daily diazepam treatment than without daily diazepam treatment. The effects of meperidine in both birds were just the opposite. Local rates of responding during daily diazepam treat-

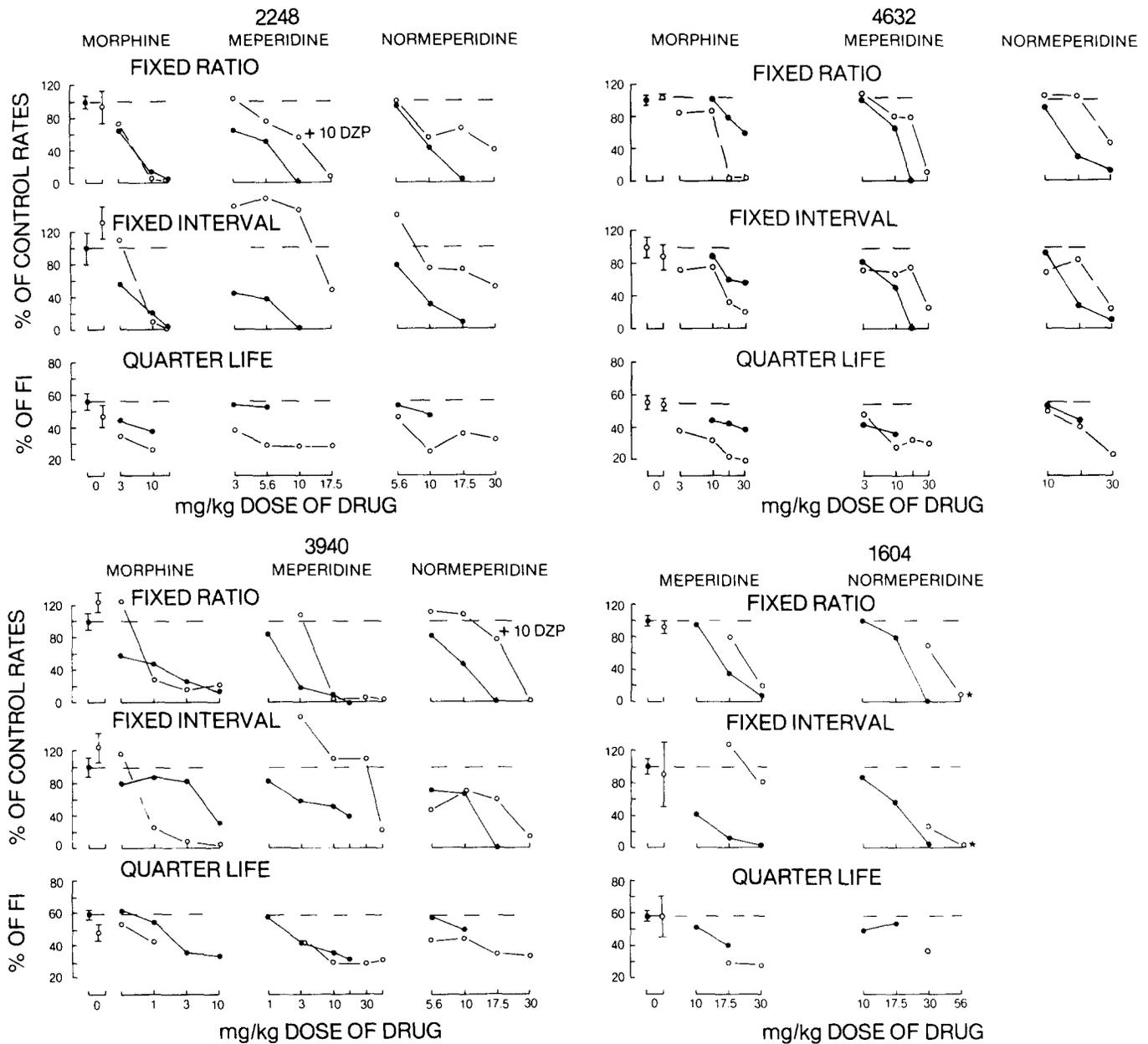


FIG. 1. Effects in four birds of morphine, meperidine and normeperidine alone (filled circles) or during chronic daily administration of 10 mg/kg of diazepam plus 60 minutes (open circles) on the rates of responding under multiple fixed-ratio 30-response, fixed-interval 5-minute schedule and on the quarter-life value. Abscissae, dose, mg/kg of drug on a log scale. Ordinates, mean rates of responding plotted as a percentage of control for the fixed-ratio component (top row in each frame) and the fixed-interval component (middle row in each frame) of the multiple schedule and the quarter-life value plotted as a percent of the fixed-interval duration (lower row in each frame). Brackets indicate \pm one standard deviation around the mean control values. The non-drug control values for response rates in each component by which these values are plotted in the figure are shown in Table 1. Each filled point is the mean of two or more determinations of each dose, whereas usually only one determination of each drug dose was made during daily administration of diazepam. The order of dose administration was mixed during each phase of the experiment except that birds 2248, 1604 and 3904 had all dose-effect curves in the absence of diazepam determined first, then the dose-effect curves determined during daily diazepam. Bird 4632 had the dose-effect curves during daily diazepam determined first. Bird 1604 died within a day after receiving the 56 mg/kg dose of normeperidine during daily diazepam treatment (noted by the asterisk), and the effects of morphine had not been determined by that time.

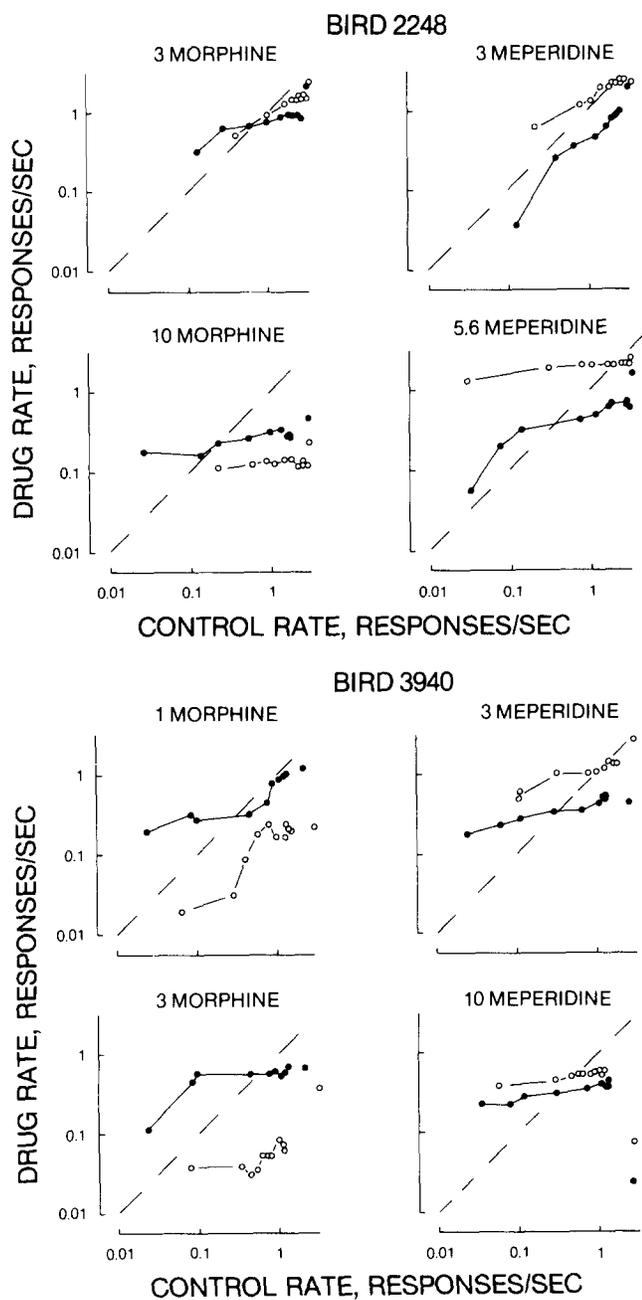


FIG. 2. Effects of two doses of morphine and two doses of meperidine on the local rates of responding within the fixed-interval and on the fixed-ratio for two representative birds. The rates after administration of the narcotics are plotted as a function of the control rates from water injection sessions. The control treatments during diazepam were diazepam orally one hour before testing, followed by an intramuscular injection of distilled water 10 minutes before testing. Filled points show the effects of narcotic alone, whereas the unfilled points show the effects of the narcotic when the bird is receiving daily treatment with diazepam. Points above and to the left of the last diagonal line indicate rate increases compared to the control values; points below and to the right indicate rate decreases. Note that both doses of morphine produce greater decreases of responding during diazepam treatment, whereas both doses of meperidine were attenuated by diazepam treatment. The fixed ratio rates are shown on the right as the unconnected points in each frame.

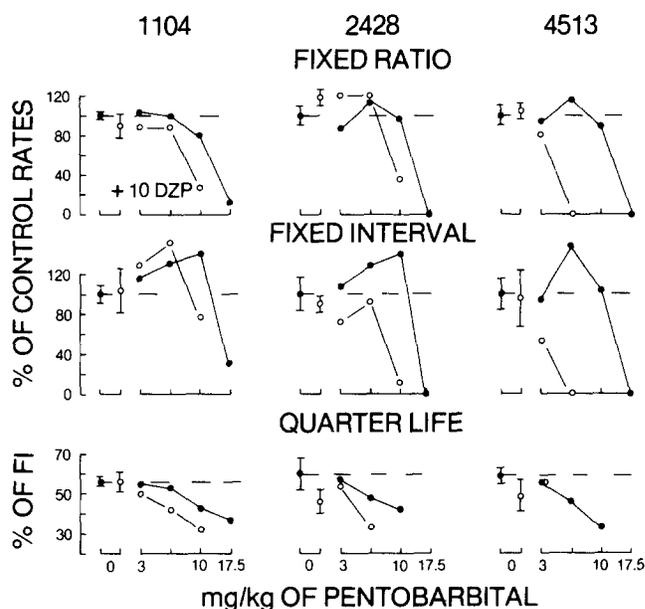


FIG. 3. Effects of pentobarbital on multiple-schedule performance in three birds alone (filled circles) and during daily diazepam treatment (unfilled circles). Further details as with Fig. 1. Note that daily diazepam treatment shifted the dose-effect curves for pentobarbital to the left in both components of the multiple schedule in all three birds. The dose-effect curves were determined first during the daily diazepam treatment.

ment were always higher than similar local rates of responding without daily diazepam treatment. Thus, irrespective of the control rates of responding exhibited in the local segments of the FI schedule, daily diazepam treatment enhanced morphine's rate-decreasing effects, whereas meperidine's effects were attenuated by daily diazepam treatment.

Effects of Pentobarbital and *d*-Methadone

Figure 3 shows the effects of pentobarbital in three birds with and without daily administration of 10 mg/kg of diazepam. Without daily administration of diazepam, intermediate doses of pentobarbital (5.6 and 10 mg/kg) increased FI responding and 17.5 mg/kg of pentobarbital decreased responding in both FR and FI components. During daily administration of 10 mg/kg of diazepam given 60 minutes before the test session, doses of 10 and even 5.6 mg/kg of pentobarbital decreased responding in FR and FI schedules. Thus, the daily administration of diazepam, which had no effect on FR responding or FI responding in any of the three birds (because of the development of tolerance to the acute effects of 10 mg/kg of diazepam), markedly enhanced the behavioral suppressing effects of doses of pentobarbital. Pentobarbital also produced a dose-related decrease in FI quarter-life value in all three birds and this effect was enhanced by daily administration of diazepam.

Twenty mg/kg of *d*-methadone produced complete suppression of responding in both components of the multiple schedule in all three birds, whereas 10 mg/kg had slight effects on rates in both components. In two of the birds, birds 1104 and 4513, daily administration of diazepam had no effect on the *d*-methadone dose-effect curve. However, in the

third bird, bird 2428, marked suppression of behavior was produced in both schedule components by 10 mg/kg of *d*-methadone when given in conjunction with 10 mg/kg of diazepam 60 minutes before the test session. Thus, like morphine, *d*-methadone's effects either were not affected by 10 mg/kg of diazepam or were enhanced.

DISCUSSION

The present study shows that daily administration of diazepam shifted the dose-effect curves for normeperidine and meperidine to the right, whereas the dose-effect curves for morphine, pentobarbital and *d*-methadone were either shifted to the left or not affected. The effects of meperidine without diazepam treatment are similar to those previously reported [29]. In that study, the behavioral effects of meperidine were not antagonized by naloxone and did not show methadone-induced cross tolerance. The interpretation was that meperidine produced its behavioral effect by a mechanism other than an opioid receptor interaction. The present study supports that conclusion in that the behavioral effects of meperidine in the present study were attenuated by daily administration of diazepam, whereas the behavioral effects of morphine, effects that have been shown to be antagonized by naloxone [32], were either not altered or enhanced by daily administration of diazepam. The behavioral effects of normeperidine without daily diazepam treatment were similar to those previously reported for pigeons responding under a similar schedule [19]. In that study the behavioral effects of normeperidine were not antagonized by naloxone, thus indicating that the behavioral effects of normeperidine were not due to an interaction with an opioid receptor.

The behavioral suppressant effects of meperidine were attenuated by acute doses of pentobarbital and, in some animals, acute doses of diazepam [20]. Normeperidine's behavioral effects could also be attenuated by acute doses of diazepam, but not to the extent that they could be by pentobarbital or clonazepam [27]. These studies suggested that the behavioral effects of meperidine and normeperidine were due to the proconvulsant effects of these two phenylpiperidine drugs. The small effects previously seen with acute doses of diazepam were postulated to be due to the rate-decreasing effects of diazepam, in that attenuation of normeperidine's and meperidine's behavioral effects occurred at doses of diazepam which in and of themselves suppressed behavioral responding. The present study circumvented the rate-decreasing acute effect of diazepam by giving diazepam daily. Previous studies have shown that many of the effects of benzodiazepines show tolerance, whereas the anticonvulsant effects of benzodiazepines generally do not show the same development of tolerance [8].

The fact that the behavioral effects of *d*-methadone and pentobarbital were not shifted to the right by daily administration of diazepam, but rather either were unaffected or were shifted to the left, suggests that the daily treatment with diazepam did not produce a nonspecific tolerance development to general depressants such as pentobarbital or other opioids with non-opioid behavioral effects. Previous re-

search has shown that the behavioral effects of *d*-methadone are not antagonized by naloxone [28]. Thus, *d*-methadone produces behavioral effects through a mechanism other than interaction with an opioid receptor. The fact that diazepam shifted the dose-effect curves of meperidine and normeperidine but not those of *d*-methadone indicates that the non-opioid effects of these two different kinds of drugs are produced by a different mechanism.

The present research does not indicate the mechanism by which meperidine and normeperidine produce their non-opioid behavioral effects, although previous research can eliminate several of the previously proposed hypotheses. First, the behavioral effects of meperidine cannot be due to normeperidine since normeperidine is less active than meperidine and inhibition of meperidine's metabolism by SKF-525A leads to enhancement of meperidine's behavioral effects rather than attenuation, as might be expected if normeperidine were the active entity [19]. Likewise, since similar non-opioid effects are produced by alphaprodine and ethoheptazine, two analogs of meperidine which could not be metabolized to normeperidine, the non-opioid effects cannot be attributed to normeperidine [18,21]. Second, the non-opioid effects of these phenylpiperidine analgesics cannot be attributed to the fact that meperidine blocks the serotonin reuptake system [33]. The evidence for this conclusion is that the behavioral effects are also produced by agents such as anileridine, alphaprodine and ethoheptazine which are not reported to block serotonin reuptake [18,21]. Also, the behavioral effects of meperidine and related analogs are not affected by chronic daily administration of clorgyline, a monoamine oxidase inhibitor [24]. Potentiation of meperidine's behavioral effects would be expected if those effects were being produced by blocking serotonin reuptake. Third, there is also little evidence that meperidine has *in vivo* anticholinergic effects since meperidine was not able to antagonize the effects of cholinergic agonists [16, 23, 25]. The present results, coupled with the previous report that meperidine's and normeperidine's behavioral effects could be attenuated by pentobarbital [20,21] suggest that the non-opioid behavioral effects of meperidine and related analogs might be due to an interaction with the GABAergic neurotransmitter system. Both the benzodiazepines and the barbiturates are thought to enhance GABAergic neurotransmission [2,11]. Thus, it might be suggested that the non-opioid behavioral effects of meperidine are due to the opposite mechanism of action, i.e., that meperidine and related analogs impair GABAergic neurotransmission. Further work should explore such a hypothesis for the non-opioid behavioral actions of meperidine and related analogs.

ACKNOWLEDGEMENTS

The author thanks Barbara Gau and Cedonia Edwards for their technical assistance, Jack Clary for help with the illustrations, the drug companies which supplied drugs used in this study, and the helpful discussions with Richard Carter and Linda Dykstra.

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