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Effects of Profadol on Operant Behavior in the Pigeon[1]

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LEANDER, J D *Effects of profadol on operant behavior in the pigeon* PHARMAC BIOCHEM BEHAV **16**(3) 487–490, 1982 —The effects of profadol were determined on the key pecking of pigeons under the control of a multiple fixed-ratio, fixed-interval schedule of grain presentation The effects of naloxone and pentobarbital on the behavioral suppression produced by profadol were also determined Profadol (0 64–10 mg/kg) decreased responding under both schedule components, and the decrease in responding could not be reversed by either naloxone or pentobarbital A moderate dose of profadol (1 25 mg/kg) was ineffective as an antagonist of morphine (20 mg/kg) Profadol does not produce its behavioral effects in pigeons by an action with a naloxone-sensitive opioid receptor and its non-opioid behavioral effects are dissimilar to those of previously studied meperidine-like phenylpiperidine analgesics

Profadol Naloxone Operant behavior Pigeons

PROFADOL (CI-572) is a congener of the phenylpiperidine analgesic meperidine [22] In contrast to meperidine, which is a morphine-like opioid, profadol is considered a partial agonist [7,23] In man, profadol is one-half to one-third as potent as morphine as an agonist, and is 1/50th as potent as nalorphine as an antagonist in precipitating narcotic abstinence [7] Humans identify profadol as producing morphine-like subjective effects [7], as do rats and squirrel monkeys in morphine-discrimination experiments [20,21] The morphine-like discriminative effects of profadol in squirrel monkeys can be antagonized by low doses of naloxone [20] and nalorphine antagonizes the analgesic effects of profadol [23] Likewise, naloxone and nalorphine can precipitate an abstinence syndrome in humans maintained on large doses of profadol [7] In rats responding under a shock-postponement schedule, profadol increases the rates of responding at the 8 mg/kg dose and decreases responding at 32 mg/kg [6] Both these rate-increasing and rate-decreasing effects of profadol are antagonized by naloxone [6]

However, some of the effects of profadol differ from those of meperidine For example, rather than depressant effects, mild signs of excitation progress to tremors and clonic convulsions with lethal doses of profadol in rats [23] Also, profadol alone has no effects on locomotor activity in rats over the dose range of 0 5 to 64 mg/kg, whereas if administered concurrently with naloxone, profadol produces a marked increase in activity [6] Thus these data suggest that profadol has some effects on behavior that are not mediated by its "partial agonist activity" at an opioid receptor

Meperidine and several congeners of meperidine have been shown to produce various non-opioid effects Their effects on schedule-controlled responding of pigeons and rats are either not antagonized by the narcotic antagonists naloxone or cyclazocine or are only antagonized marginally [8, 9, 11, 16, 18] and do not exhibit methadone-induced cross tolerance [8,16] Pentobarbital, however, attenuates the behavioral suppression produced by meperidine and several of the congeners [10,11], suggesting that the non-opioid effects of these agents may be produced by their proconvulsive actions [1]

Profadol has a pyrolidine ring structure, whereas meperidine and the other analogs previously studied have a piperidine ring structure The 4-phenylpiperidine analog (Compound VII in [17] and LY27372 in [13]) of profadol has recently been studied on schedule-controlled responding in pigeons [13] Though its analgesic effects in rodents are opioid in nature [17], the effects on schedule-controlled responding were not antagonized by naloxone or attenuated by pentobarbital [13] Thus, the 4-phenylpiperidine analog of profadol exhibited behavioral effects different from both morphine-like and meperidine-like analgesics These observations with the 4-phenylpiperidine analog and the close structural resemblance between it and profadol suggest that profadol may exhibit non-opioid effects which are dissimilar to both morphine and meperidine on schedule-controlled responding Thus the purposes of the present experiment were to determine the effects of profadol on schedule-controlled responding, to determine if naloxone would antagonize the behavioral suppression produced by profadol, and to deter-

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mine if pentobarbital would attenuate the behavioral suppression produced by profadol, and to determine if profadol would antagonize the effects of morphine on schedule-controlled responding

METHOD

Animals

Male adult white Carneaux pigeons were housed in individual cages and maintained at approximately 80 percent of their free-feeding weight by pigeon grain presented during experimental sessions and by post-session feedings Oyster shell grit was freely available in the home cages and water was freely available in both the home cage and the test cage All the birds had extensive histories with the multiple schedule of grain presentation and with injections of diverse psychoactive drugs (narcotics, narcotic antagonists, and various depressants) prior to the beginning of this experiment There was no evidence to suggest that this history has any determining effects on present results

Apparatus

The experimental chambers were sound-attenuating and ventilated [3] The experimental space was 29 cm high × 27 cm wide × 29 cm long A translucent plastic response key, 2 cm in diameter, was mounted in the center of a wall inside the chamber, 22 cm above the wire mesh floor The response key could be transilluminated by red or blue lights A peck with a minimal force of 0 15 operated the key and defined a response Below the response key was a rectangular opening through which the pigeon could be given access to mixed grain The experimental space was illuminated by a 7 5 Watt bulb During 4-sec grain presentation cycle, all lights in the test chamber were off except one illuminating the grain Relay programming and recording equipment in an adjacent room controlled events and recorded the data

Procedure

The multiple fixed-ratio 30 response, fixed-interval 5-min schedule (mult FR-30, FI-5) can be described in the following manner [3] When a blue light transilluminated the response key, the 30th response produced the 4-sec grain presentation (FR-30) When a red light transilluminated the response key, the first response to occur after 5 min elasped produced grain presentation (FI-5) A 40-sec limited hold was in effect in both components, i e , in the FR component, the bird had 40 sec to emit the 30 responses, and in the FI component, the bird had up to 40 sec after 5 min had elasped to respond and produce grain presentation Schedule components alternated after each grain presentation or when the limited hold elasped Sessions were conducted Monday through Friday for 1 hr each day, and began in the FR component

Administration of Drugs

The drugs used and the forms in which doses were calculated are morphine sulfate, pentobarbital sodium, naloxone hydrochloride (donated by Endo Laboratories, Inc , Garden City, NY) and profadol hydrochloride (donated by Warner-Lambert/Parke-Davis, Ann Arbor, MI) All drugs were dissolved in distilled water, and distilled water was used for control injections All injections were administered in the breast muscle in a volume of 1 ml/kg, 10 min before the 60-min test session began When two injections were scheduled, they were administered in opposite sides of the breast muscle in no systematic order Injections of drugs were administered no more frequently than twice a week (usually on Tuesdays and Fridays) One or two injections of distilled water were given on Thursdays of each week, and the data obtained on Thursdays served as non-drug control data

Measurement of Drug Effects

Average rates of responding for each individual bird during the FR and FI components were computed in responses per sec from digital counters and elapsed-time meters Drug effects were then calculated as a percent of the mean control values obtained on sessions when distilled water was injected as the vehicle control (usually Thursdays) The responses within successive tenths of the FI-5 were used to calculate a quarter-life value, a statistic that is independent of response rate and is used to describe quantitatively the positively accelerated pattern of responding that occurs during the FI schedule The quarter-life value is defined as the percentage of the FI required for 25 percent of the total responses to be emitted [4,5]

RESULTS

The average non-drug rates of responding under the FR component of the multiple schedule were high (ranging from 1 8 to 3 6 responses per sec in individual birds) as compared to the average non-drug rates of responding maintained by FI component (ranging from 0 39 to 1 4 responses per sec in individual birds) The non-drug FI quarter-life values ranged from 44 to 61 percent which indicated that the typical, positively accelerated pattern of responding was generated by the FI schedule This pattern is characterized by a very low rate of responding early in the FI component, followed by a transition period and then a fairly high rate of responding just prior to the end of the FI and subsequent grain presentation These non-drug control performances are similar to those previously reported for pigeons and other species responding under similar schedules [3, 8 13, 16]

Figure 1 shows the effects of profadol alone and the highest dose of profadol with 3 doses of naloxone Increasing doses of profadol produced a dose-related decrease in the rates of responding in both schedule components with a greater tendency to decrease FR rates than FI rates The 10 mg/kg dose of profadol produced an average FR rate of 10 percent of control whereas the FI rate was 44 percent of control Profadol also decreased the average quarter-life values which indicated a disruption of the usual positively-accelerated pattern of responding Naloxone did not antagonize the effects of 10 mg/kg of profadol at any dose tested, and the 10 mg/kg dose of naloxone actually appeared to potentiate the behavioral suppressing effects of profadol

Figure 2 shows the effects of two doses of pentobarbital when administered alone (left) and when administered simultaneously with the 10 mg/kg dose of profadol, which markedly decreases responding when administered alone (far right side figure above the letter P) Pentobarbital alone increased responding in the FI component, especially at the 5 mg/kg dose These doses of pentobarbital, however, did not affect the behavioral suppressing effects of profadol That is, pentobarbital did not attenuate or potentiate the effects of 10 mg/kg of profadol

In 4 birds, 20 mg/kg of morphine decreased rates of responding in both schedule components (mean=49 percent of

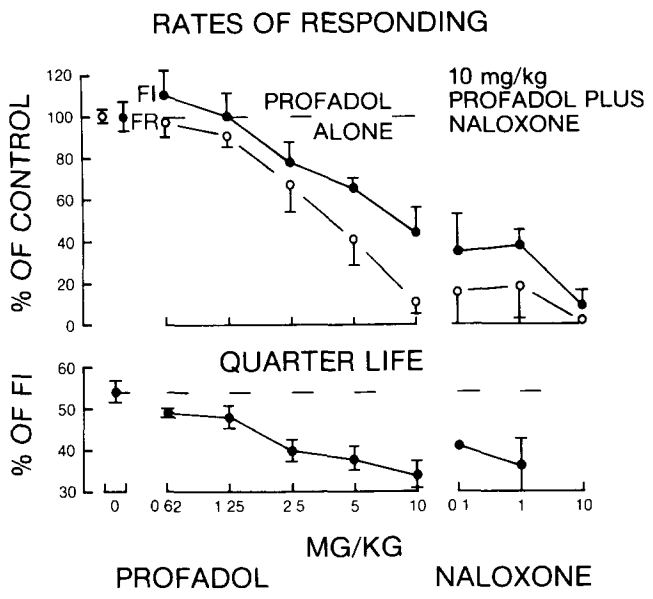

FIG 1 Mean effects of profadol alone (left) and the highest dose (10 mg/kg) of profadol in combination with 3 doses of naloxone (right) on the rates of responding in the FR (○) and FI (●) components (upper frame) and the FI quarter-life value (lower frame) Abscissae dose of drug log scale Ordinates rates of responding as percent of control rates (FR=2 41 responses/sec, FI=0 8 response/sec) and FI quarter-life values as percent of the FI Quarter-life values were not calculated if FI rates were less than 0 1 response/sec since such a low response output would make the calculated quarter-life value unreliable The profadol alone points are the mean (±S E M) of two determinations in each of three birds The naloxone data are the mean of one determination in each of three birds

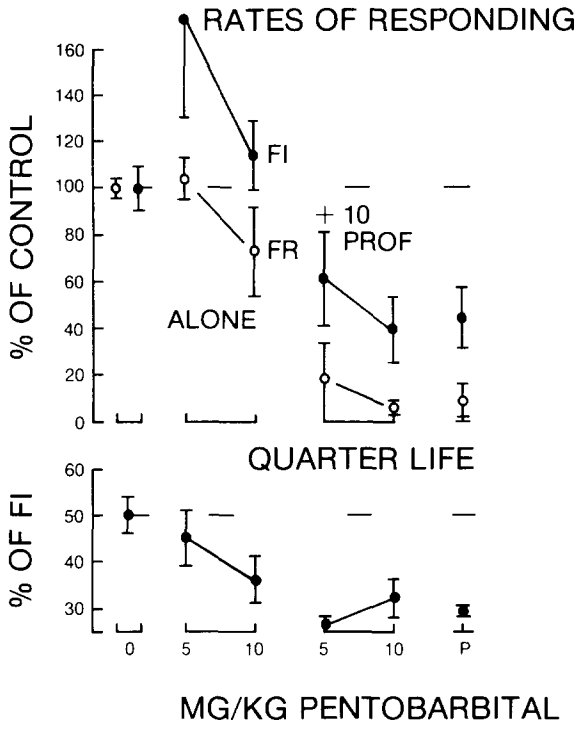

FIG 2 Mean affects of pentobarbital alone (left) and in the presence of 10 mg/kg of profadol (middle) and the effects of 10 mg/kg of profadol alone (right, above P) Pentobarbital alone data points are the mean (±S E M) of single determinations in three birds, whereas all the other data points are the mean (±S E M) of six birds Control FR rates=3 16 responses/sec, FI rates=0 66 response/sec Other details as with Fig 1

control in FR and 15 percent in FI) and decreased the quarter-life from the control value of 60 percent of the FI to 35 percent of the FI A threshold dose of profadol (1 25 mg/kg) for producing effects alone (Fig 1) was tested in combination with the 20 mg/kg of morphine The 1 25 mg/kg dose of profadol did not antagonize the effects of 20 mg/kg of morphine but rather appeared to potentiate morphine's effects (data not shown)

DISCUSSION

Profadol decreased the rates of schedule-controlled responding and disrupted the patterning under the FI component These effects were not antagonized by naloxone or attenuated by pentobarbital Thus the effects of profadol differ from the effects of meperidine, normeperidine and azabicylane [9, 10, 11, 16] The latter three drugs produce decreases in the rates and patterning of schedule-controlled responding over approximately the same dose range as profadol, and naloxone is unable to antagonize this effect However, in contrast to the effects seen with profadol, pentobarbital attenuates the rate-decreasing effects of meperidine, normeperidine and azabicyclane [10,11], suggesting that the non-opioid, rate-decreasing effects of these drugs were due to a proconvulsive action that these have [1] The lack of attenuation of profadol's effects by pentobarbital suggests that this rate-decreasing effect is not due to a proconvulsive action, and the lack of antagonism by naloxone indicates it is not due to an opioid agonist action Thus the effect of profadol on schedule controlled behavior is non-opioid in nature, but is not similar to the non-opioid, proconvulsive action of meperidine-like drugs The different effects obtained with the different analogs of meperidine in pigeon suggest that their behavioral effects can be fit into three categories (1) opioid, (2) non-opioid proconvulsive, and (3) non-opioid nonproconvulsive An example of an analog fitting primarily in category 1 is fentanyl [8], in category 2 is meperidine [8, 9, 16] and in category 3 is profadol (present paper) This non-opioid action of profadol is so prominent in the pigeon that neither the opioid agonist activity nor antagonist activity could be demonstrated in the present study In the rat, profadol produces naloxone antagonizable effects on operant behavior maintained by a shock-postponement schedule [6] It is not clear whether the difference between the avoidance behavior study in rats and the present study with pigeons responding under a food schedule is due to a real species difference or due to the different schedules and reinforcers maintaining the behaviors It should be emphasized that, although these effects on schedule-controlled responding were not antagonized by naloxone, it does not mean that other effects of profadol in the pigeon would not be antagonized by naloxone Thus,

whether or not an effect of profadol (or any meperidine analog) is antagonizable by naloxone is dependent upon both what species it is tested in and what the specific effect is This point is clearly shown in the report [12] that naloxone in rats antagonized the analgesic effects of meperidine but not the effects of meperidine on schedule-controlled responding

The doses of naloxone used in the present study do not have effects of their own on the schedule-controlled responding of the pigeon since doses greater than 10 mg/kg of naloxone alone are required to affect responding [2,19] However, a 0 1 mg/kg dose completely antagonizes the behavioral-suppressing effects of mu-type opioid agonists (morphine, fentanyl, *l*-methadone, and phenazocine [2, 14, 15,19]), whereas 10 mg/kg of naloxone is required to antagonize the kappa-type agonists, ketazocine and ethylketazocine [14] Thus for the pigeon, an adequate range of naloxone doses was tested in the attempt to antagonize profadol's effects Likewise, the lack of antagonist activity for profadol in antagonizing the effects of 20 mg/kg of morphine is not due to the dose of morphine Narcotic antagonists such as naloxone, cyclazocine and even the recently reported phenylpiperidine narcotic antagonists readily antagonize the effects of similar doses of morphine on schedule-controlled responding in the pigeon [2, 13, 19]

The effects of profadol on schedule-controlled responding are identical to those reported for the 4-phenylpiperidine analog [13] suppression of responding by identical doses, not antagonized by naloxone, not attenuated by pentobarbital, and devoid of morphine antagonist activity at a threshold dose Profadol and the 4-phenylpiperidine analog are identical in chemical structures except that profadol has a pyrolidine ring (5-member nitrogen-containing ring), whereas the analog has a piperidine ring (6-member nitrogen-containing ring) structure It is surprising that apparently the change in ring size had no effect on the behavorial effects of these two drugs in the pigeon

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