Pharmacology Biochemistry & Behavior, Vol. 16, pp. 271–278, 1982. Printed in the U.S.A.

Interaction of Methadone and Pentobarbital on Chained Fixed-Interval Performance in Pigeons[1]

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Received 24 November 1980

JENSEN, M. A. AND T. I. THOMPSON. *Interaction of methadone and pentobarbital on chained fixed-interval performance in pigeons.* PHARMAC. BIOCHEM. BEHAV. 16(2) 271–278, 1982.—The effects of methadone, pentobarbital, and their combination were examined in pigeons key pecking under a chained FR 3 (FI 30 sec) schedule of food presentation. The delivery of grain followed the completion of three 30-second fixed-interval components associated with different colored key lights. Intramuscular injections of methadone alone produced small response rate increases at low doses (0.25 and 0.50 mg/kg) and a dose-dependent decrease in key pecking rates at high doses (1.0 and 2.0 mg/kg). Pentobarbital (2, 4, and 8 mg/kg) produced a dose-dependent increase in response rates; 16 mg/kg pentobarbital markedly reduced or abolished responding. Combinations of these doses of methadone and pentobarbital produced increases in key pecking rates greater than the rate increases produced by methadone alone, and in four of the seven subjects, greater than the rate-increasing effects of pentobarbital alone. Changes in overall response rates were a function of changes in pause time (minutes from food delivery to the first key peck) and running response rates (total key pecks divided by session length minus pause time). Responding in the individual FI 30 sec components varied with the dose of methadone; doses greater than 0.25 mg/kg produced a dose-related decrease in key pecking rates in the initial component and small increases in the middle and terminal components. Pentobarbital (2, 4, and 8 mg/kg) produced large dose-related increases in key pecking rates in the initial and middle components. The largest increase in response rate was observed in the middle component after the combination of drugs was administered. Pentobarbital's rate-increasing effect under the chained schedule attenuated the rate-reducing effect of methadone when administered in combination.

Pigeons Methadone Pentobarbital Chained schedule Fixed-interval schedule

THE behavioral effects of combinations of narcotics and narcotic antagonists have been examined using the schedule-controlled operant performance of the pigeon [6, 7, 10, 20, 21, 33]. However, less is known about the effects of combinations of narcotics with other drugs that affect behavior. Smith [26] found that the joint behavioral effects of d-amphetamine and morphine were predictable from the effects of each drug alone. Key pecking rate decreases in pigeons produced by morphine were attenuated if d-amphetamine alone had increased responding and were enhanced if d-amphetamine alone had decreased responding. However, the joint effects of pentobarbital and morphine are not always predictable from the effects of each drug alone [26]. Doses of pentobarbital which increased key pecking rate maintained by a fixed-interval schedule of food presentation did not attenuate the rate-decreasing effects of morphine on key pecking maintained by the fixed-interval schedule.

Low doses of morphine [20] and methadone [21] frequently increase response rates under the fixed-interval (FI) component of a multiple fixed-interval fixed-ratio schedule (mult FI FR) and decrease response rates in both the FI and FR components at higher doses. McGuire and Thompson [18] reported that the rate-decreasing effects of methadone on overall response rates were attenuated when key pecking was maintained under second-order FI schedules associated with strong discriminative stimuli or conditioned reinforcers. Performance in pigeons under a brief stimulus schedule, FR 3 (FI 30 sec), was resistant to the effects of methadone whereas behavior maintained by a tandem schedule, FR 3 (FI 30 sec), with no associated stimulus changes, was easily disrupted. The effects of methadone on key pecking maintained by an equal-valued chained schedule was affected in an intermediate fashion.

McGuire and Thompson's data [18] suggest that environmental events can alter the effects of methadone on operant performance maintained by fixed-interval reinforcement schedules. To further analyze the effects of methadone on

[1]This research was supported by National Institute on Drug Abuse Grant DA00332.

[2]This research represents a portion of the doctoral dissertation of M. A. J. submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Psychology at the University of Minnesota.

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fixed-interval performance in the presence of exteroceptive stimuli associated with varying probabilities of reinforcement, the present study examined effects of methadone on key pecking maintained by a second-order chained fixed-interval schedule of food presentation, chain FR 3 (FI 30 sec) schedule. Under this schedule, grain presentation followed completion of three 30-second FI components, each associated with a different stimulus. The component stimuli have been shown to serve as both conditioned reinforcing stimuli for behavior in a preceding interval and discriminative stimuli that control a rate and pattern of responding appropriate to the component schedule [11].

Despite the widespread use of chronic methadone in the treatment of heroin dependence and the concurrent use of other drugs, including barbiturates, by methadone patients [32], relatively little is known about the combined behavioral effects of these compounds. Thus, the behavioral effects of pentobarbital, a prototypic barbiturate, alone and in combination with methadone, were examined.

METHOD

Subjects

Seven experimentally naive adult male White Carneaux pigeons maintained at 80% of their free-feeding weights served as subjects. The birds' weights ranged from 411 to 504 grams. The birds were individually housed in a colony room maintained at 24°C with 24-hour illumination. Water and grit were continuously available in the home cages.

Apparatus

Four pigeon operant test chambers were ventilated and sound-attenuated cubicles (Small Universal Cubicle 132-03, BRS/LVE, Beltsville, MD) equipped with a 2-key pigeon intelligence panel (Model 141-15, BRS/LVE) and feeder (Model 114-10, BRS/LVE). The chambers were illuminated by white house lights (1820 bulb), and white masking noise was present continuously. In each chamber the response key to the right of the feeder was operable and could be transilluminated by a red, green, or white light. The left key was dark, and pecks on that key had no programmed consequences. During food delivery, the food magazine was illuminated, and the right response key light was extinguished. Programming and data collection were performed by commercially available electromechanical equipment, cumulative recorders, and counters located in an adjacent room.

Procedure

The subjects were hand-shaped to peck the right response key, producing 3-seconds access to mixed grain. For the next 3 or 4 sessions the subjects received 50 food presentations per session on a continuous reinforcement schedule (i.e., each peck produced a 3-second access to food). When the key peck was established, the schedule was changed to a fixed-interval 10 second (FI 10 sec) schedule of food presentation. In the presence of a white key light, food was delivered following the first key peck after 10 seconds had elapsed from the preceding food delivery. Over the next several sessions a 2-component and finally a 3-component chained FI 10 second schedule were introduced; i.e., chain FR 2 (FI 10 sec) and chain FR 3 (FI 10 sec), with different key lights associated with each component FI schedule. Under the chain FR 3 (FI 10 sec) reinforcement schedule, a key peck after 10 seconds in the presence of a red key light produced a green key light; a key peck in the presence of the green light produced a white light; and in the presence of the white light, a key peck after 10 seconds produced access to grain. After stable performance developed under the chain FR 3 (FI 10 sec) schedule, the FI value in each component was increased from 10 to 30 seconds over 8 sessions. The birds were exposed to the terminal contingencies, chain FR 3 (FI 30 sec), for 3 to 3.5 months prior to the initiation of drug administration to stabilize baseline rates and allow adaptation to vehicle injections. Subjects were placed in the darkened operant test chamber 15 minutes before the start of each 45 minute session. Experimental sessions were conducted at the same time each day, 7 days a week.

Drugs

After stable performance was established, as determined by 5 consecutive sessions with no systematic increase or decrease in overall key peck rate and overall rates of key pecking during at least 4 of the 5 sessions within ±10% of the mean rate over the 5 sessions, dose-response curves for methadone hydrochloride and sodium pentobarbital were obtained. Each subject received 0.25, 0.50, 1.0, and 2.0 mg/kg methadone hydrochloride and after completion of the methadone series, 2, 4, 8, and 16 mg/kg sodium pentobarbital; each dose was administered twice in a mixed order. Methadone or pentobarbital, dissolved in 0.9% saline, was administered intramuscularly 15 minutes prior to 45-minute test sessions. Solutions were prepared so that each dose, expressed as the salt, was administered in a constant 1 ml/kg injection volume. Saline, 1 ml/kg injection volume, was used for vehicle injections on the day preceding drug administration.

Drug injections in both drug series were separated by a minimum of 5 noninjection sessions and one vehicle control session to minimize the development of behavioral tolerance to methadone [13] and to maximize baseline stability prior to drug administration. When the stability criterion was met, as defined above, the following session constituted a saline control session. If the overall saline response rates were within ±10% of the mean of the preceding 5 sessions, drug was administered on the following day.

After dose-response curves were obtained for each drug alone, combinations of the doses of methadone and pentobarbital which had been administered alone were given to each subject. Both drugs were administered 15 minutes prior to the session, one injection into each breast muscle, with a minimum of 6 days intervening between successive drug sessions. Vehicle control injections consisted of double saline injections, one on each side, on the day preceding drug administration. Because the effect of the dose combinations was not known, some of the birds initially received low doses of methadone in combination with increasing doses of pentobarbital and the remainder received low doses of pentobarbital in combination with increasing doses of methadone. One determination at each combination was made in each pigeon except for the combination of 16 mg/kg pentobarbital with 1.0 mg/kg and 2.0 mg/kg methadone. To minimize the possibility of respiratory depression, only P-14 received these two drug combinations.

After all drug combinations had been administered to each bird, each subject received a combination of 2.0 mg/kg methadone and saline, followed a week later by a combination of 16 mg/kg pentobarbital and saline, to determine

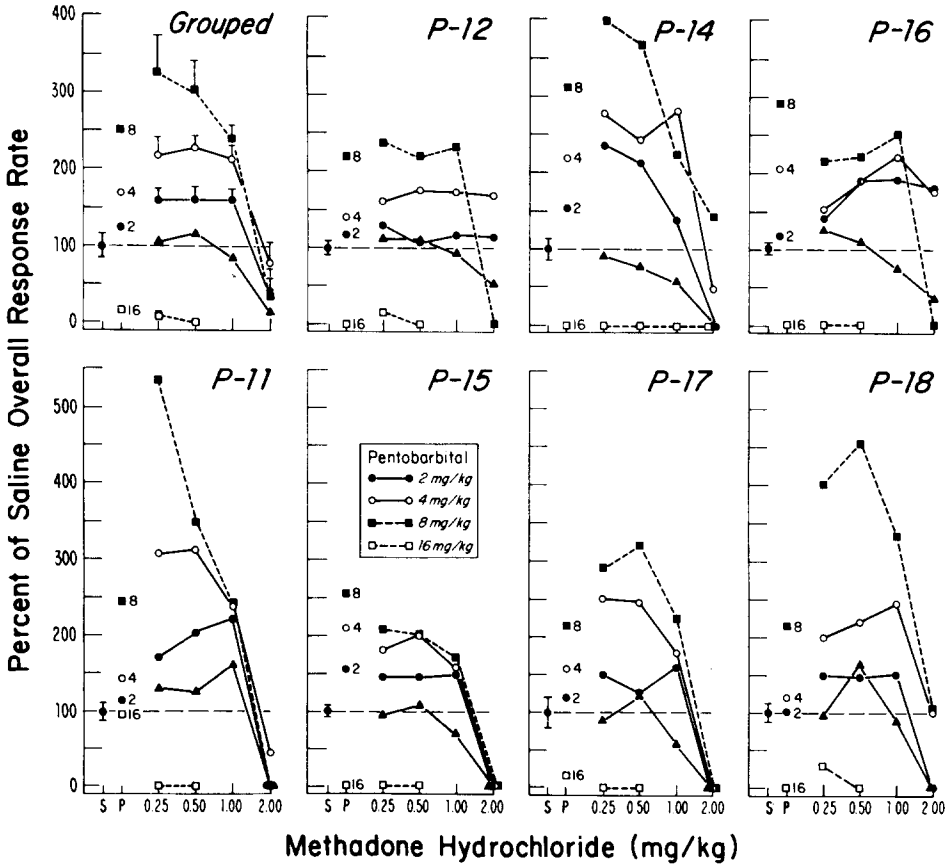

FIG. 1. Effects of combinations of methadone and pentobarbital on overall rate of key pecking under the chain FR 3 (FI 30 sec) schedule, expressed as a percentage of the saline overall response rate. The grouped dose-response curve represents the mean ± SE overall response rate for 7 birds. The point at "S" represents the mean ± SE over the saline control sessions. The points at "P" represent mean overall response rate, expressed as a percentage of saline control values obtained after the administration of pentobarbital alone. The dose-response curve indicated by ▲——▲ represents the mean overall response rate after methadone alone. Points on the individual dose-response curves represent one determination at each dose combination and the mean of 2 determinations after pentobarbital alone (points at "P") and methadone alone (▲——▲). The mean ± SD overall response rate over the 14 saline control sessions preceding drug administration is indicated by the points at "S" on the individual curves.

whether any change in sensitivity to methadone or pentobarbital had occurred since obtaining the original dose-response curves.

Data Analysis

The following dependent variables were analyzed: (1) overall key pecking rate—total number of key pecks per session divided by 45 minutes; (2) pause time—total time (minutes) between session start or reinforcer delivery and initiation of a new FI (i.e., first key peck in first FI 30 sec component); (3) running key peck rate—total number of key pecks per session divided by (45 minutes minus total pause time) [30]; (4) key pecking rate in individual FI 30 sec components—total number of key pecks in each component per session divided by number of minutes in each component. The effects of methadone, pentobarbital, and their combination were expressed as a percent of saline control values for individual subjects. Control values were the mean of the vehicle injection sessions preceding drug sessions.

RESULTS

Effects of Methadone Alone

Overall key pecking rates were increased above control values in five of the seven birds administered 0.25 or 0.50 mg/kg of methadone (triangles in Fig. 1). With the exception of P-11, 1.0 mg/kg methadone reduced key peck rates, and in all subjects 2.0 mg/kg markedly reduced or abolished responding. To assess the locus of effect of methadone on performance, running key peck rates and pause time were analyzed. The small increases in overall rates following low methadone doses were associated with increased running rates; pause time was not affected. Increases in running rate, defined as the number of key pecks per session divided by 45

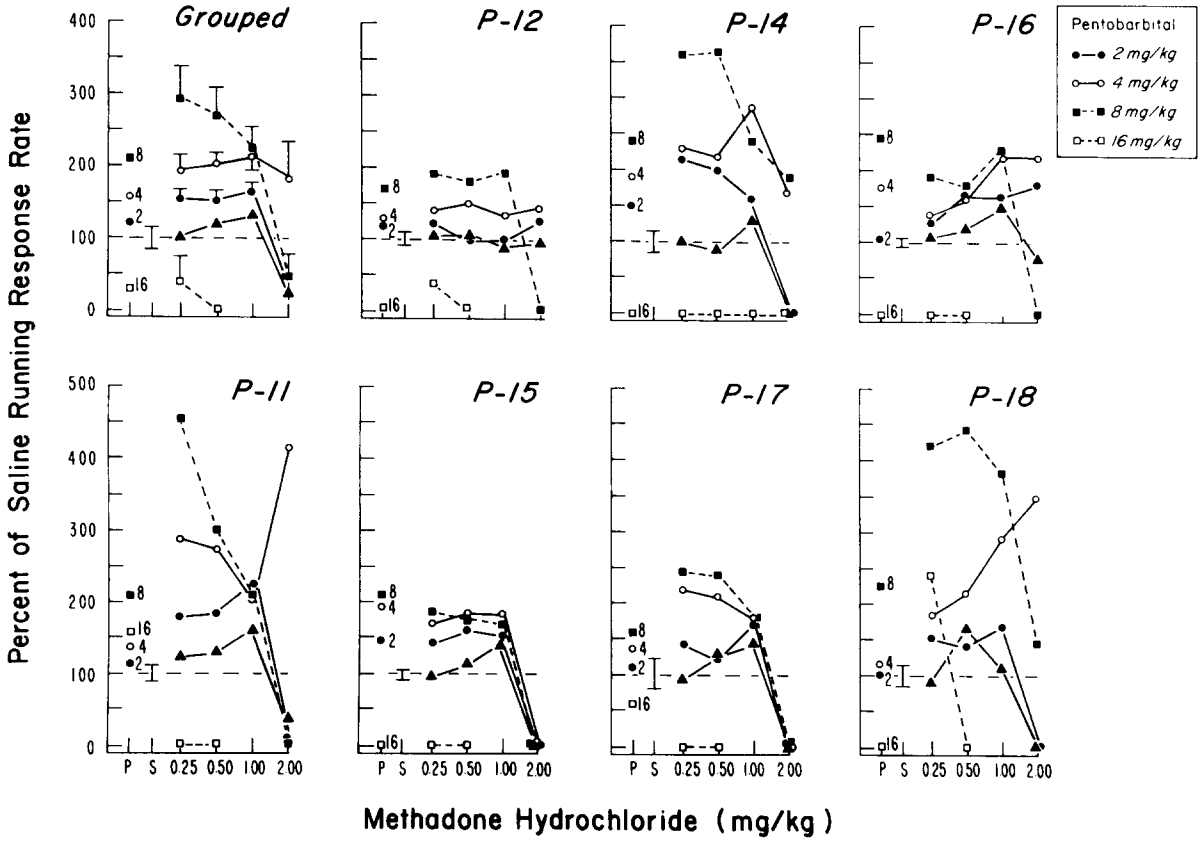

FIG. 2. Effects of combinations of methadone and pentobarbital on running response rate, expressed as a percentage of saline running response rates. Running response rate was determined by dividing the total number of key pecks per session by 45 minutes minus total pause time. See Fig. 1 legend for additional details.

minutes minus pause time, were observed in six of the seven birds with the largest increase typically occurring after 1.0 mg/kg, a dose which had an overall rate-reducing effect (triangles in Fig. 2). The reduction in overall rates after 1.0 and 2.0 mg/kg was a function of increased pausing in the first FI 30 sec components (triangles in Fig. 3). The effects of methadone on response rates in individual FI 30 sec components varied with the dose (Fig. 4). Control performance was characterized by pausing in the initial component followed by increased key pecking rate across the middle and terminal components to food delivery. At doses larger than 0.25 mg/kg methadone, rates in the initial FI 30 sec component were decreased below saline control values. Key pecking rates in the middle and terminal components were increased above saline control values after 0.50 and 1.0 mg/kg methadone; responding was markedly reduced in all components after 2.0 mg/kg methadone.

Effects of Pentobarbital Alone

Pentobarbital produced dose-related increases in overall key pecking rates in all subjects until a 16 mg/kg dose was reached, after which key pecking was markedly reduced or abolished in all but one subject (points at "P" in Fig. 1). P-11 did not peck for approximately 25 minutes after each administration of this dose but resumed pecking at a high rate for the remainder of both sessions. With the exception of 16 mg/kg, pentobarbital produced a dose-related increase in running key pecking rates (points at "P" in Fig. 2) and a small dose-related reduction in pausing (points at "P" in Fig. 3). Pentobarbital (2, 4, and 8 mg/kg) produced dose-related increases in response rates in individual FI 30 sec components with increases of 407% and 370% of saline control values in the initial and middle components compared with 192% in the terminal component (Fig. 4).

Effects of Methadone and Pentobarbital in Combination

Combinations of methadone and pentobarbital produced increases in overall key pecking rates greater than the increases produced by methadone alone, and in four of the seven birds (P-11, P-14, P-17, and P-18), greater than the rate-increasing effects of pentobarbital alone (Fig. 1). Although increases in key pecking rate above pentobarbital values were not consistently seen in the performance of the remaining three subjects, some dose combinations did result in rate increases greater than the rate increases produced by pentobarbital alone (e.g., 2 mg/kg pentobarbital with methadone in P-16). The increased overall key pecking rates produced by the combination of methadone and pentobarbital reflect increased running rates and reduced pausing in the first FI 30 sec components. Increases in running rate produced by the combination were greater than the increases in running rate produced by methadone alone, and in the

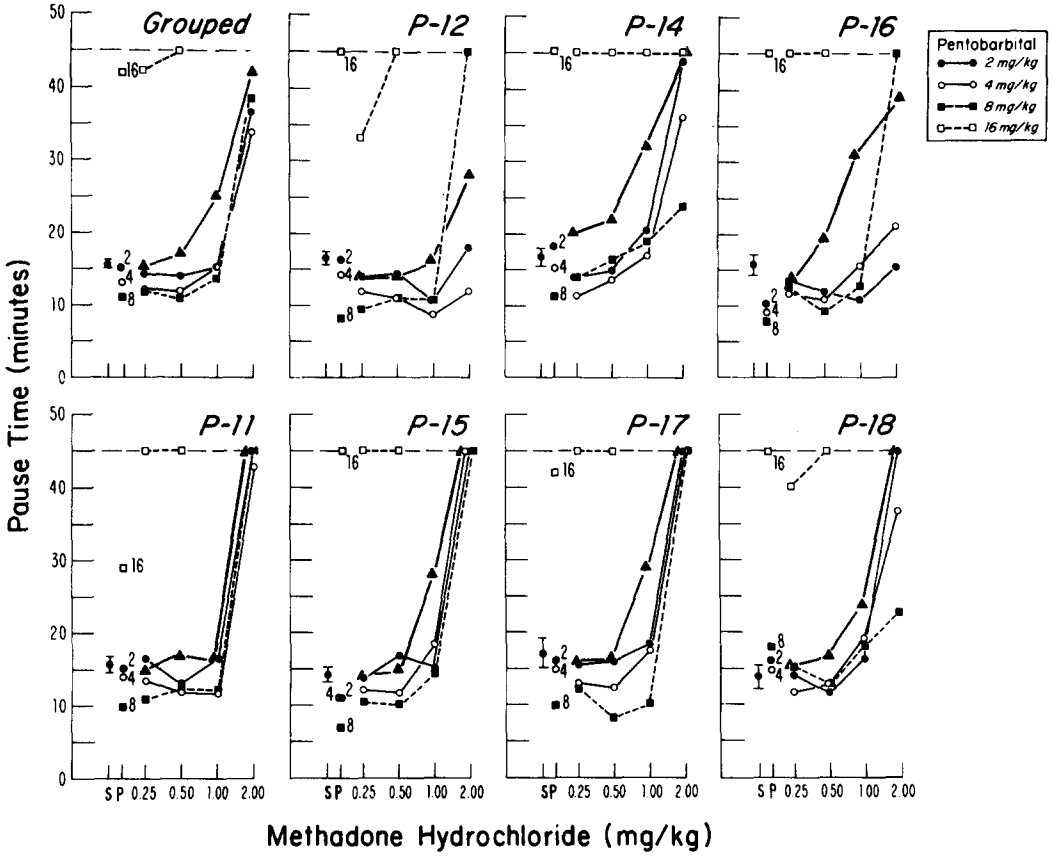

FIG. 3. Effects of combinations of methadone and pentobarbital on minutes of pausing after reinforcement. Pause time was defined by the total time (min) between session start or reinforcer delivery and initiation of a new FI (i.e., first key peck in the first FI 30 sec component). The dashed lines at 45 minutes indicate the maximum pause time due to session length. See Fig. 1 legend for additional details.

same four birds (P-11, P-14, P-17, and P-18), greater than the increases after pentobarbital (Fig. 2). Pause time was not altered or was decreased below saline values after the administration of pentobarbital and doses of methadone below 2.0 mg/kg (Fig. 3). Pausing after 2.0 mg/kg methadone was dependent on the pentobarbital dose in four of the subjects, although pausing was typically increased; 16 mg/kg pentobarbital markedly suppressed responding in all subjects when administered with any dose of methadone. Combinations of methadone and pentobarbital produced the largest increases in response rates in the middle FI 30 sec component with the largest increase in this component occurring after a combination of 8 mg/kg pentobarbital and 0.25 mg/kg methadone (Fig. 4).

DISCUSSION

The effects of acutely administered methadone on key pecking performance maintained by chained fixed-interval food reinforcement schedules in the pigeon are similar to the effects reported previously on key pecking maintained by the FI component of a mult FI FR reinforcement schedule [20]; low doses of methadone increased key pecking rates and higher doses decreased response rates. Methadone decreased overall key pecking rates in the chain FI component of a mult brief stimulus-tandem-chain reinforcement schedule; individual components of the chain schedule were not analyzed [18]. Response rate changes in individual FI components in the present study reflect the increased pausing in the initial component and increased running response rates in the middle and terminal components after methadone. The rate-increasing effects of pentobarbital on performance maintained by the chain FI schedule are consistent with the results obtained under a variety of schedule conditions [25]. The sizable response rate increases in the initial and middle components after pentobarbital suggest a rate-dependent effect commonly reported after barbiturate administration [24].

The results of the combination of methadone and pentobarbital were not expected in view of the joint effects of pentobarbital and morphine on key pecking maintained by a mult FI FR reinforcement schedule [26]. Doses of pentobarbital which greatly increased FI-maintained performance under the mult schedule did not attenuate the rate-decreasing effects of morphine on responding under the FI component. Rather, the effects were determined largely by the dose of morphine without regard to the dose of pentobarbital. In the present study, doses of methadone and pentobarbital which increased key pecking rates produced increases in key pecking rates when given concurrently, which were greater than

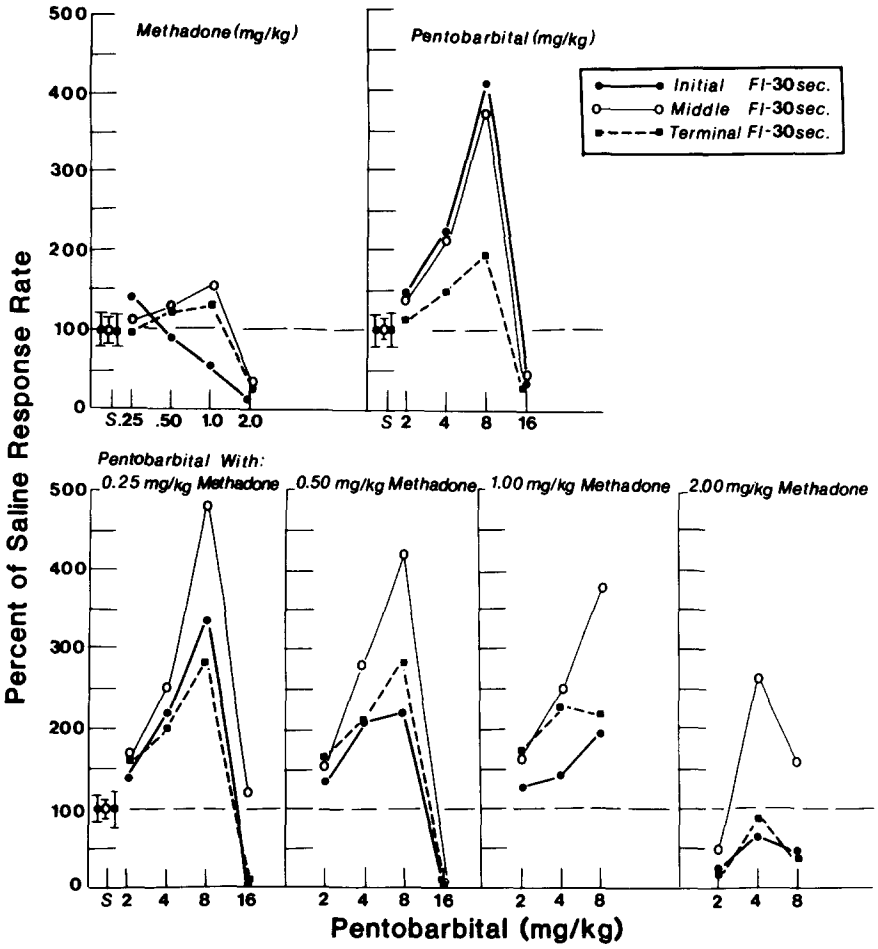

FIG. 4. Effects of methadone and pentobarbital, alone and in combination, on rate of key pecking in individual FI 30 sec components under the chain FR 3 (FI 30 sec) schedule, expressed as a percentage of the saline response rates. The grouped dose-response curves represent the mean response rate for each component for 7 birds. The points at "S" represent the mean±SE response rate for each component over the saline control sessions.

the rate-increasing effects of either drug alone. The rate-decreasing effects of higher doses of methadone were attenuated by the rate-increasing effects of pentobarbital.

There are important differences in the effects of narcotics when given in combination with either specific narcotic antagonists such as naloxone, or in combination with other behaviorally active compounds such as d-amphetamine. In both pigeons and squirrel monkeys, decreases in rate of schedule-controlled responding produced by morphine are antagonized by doses of naloxone which themselves do not have any systematic behavioral effect, and increasing doses of naloxone produce corresponding shifts to the right in the morphine dose-effect curve [3, 10, 21]. The displacement of the morphine dose-effect curve to the right when naloxone is administered with morphine is characteristic of competitive pharmacological antagonism [8,12]. d-Amphetamine can also attenuate the rate-decreasing effects of morphine, but only at doses which themselves increase responding; appropriate doses of d-amphetamine produce corresponding vertical shifts in morphine dose-effect curves [3, 21, 26]. The absence of a shift of the morphine curve to the right after d-amphetamine administration suggests the results of the combination are not attributable to competitive antagonism. Byrd [3] and McMillan [21] suggest that the effect of administering morphine and d-amphetamine together depends on the rate-increasing effect of d-amphetamine.

In the present study, the absence of a shift in the methadone dose-response curve to the right when pentobarbital was administered with methadone suggests that the results are not due to competitive antagonism. The grouped dose-response curve is displaced upward by a relatively constant amount after administration of methadone with doses of pentobarbital below 16 mg/kg (Fig. 1).

Pentobarbital and methadone are metabolized by the hepatic microsomal enzyme system and act as inducers of these drug metabolizing enzymes [5, 16, 17]. Alterations in the biotransformation of these two compounds as a result of their concomitant administration might be a possible mech-

anism responsible for these findings. Phenobarbital, which stimulates the biotransformation of methadone, decreases the analgesic property of methadone [15]. However, development of tolerance in rats to the analgesic effect of methadone required pretreatment with phenobarbital for four days (or the addition of methadone in the drinking water for two weeks). Chronic oral administration of methadone resulted in its own enhanced biotransformation and potentiated the rate of pentobarbital metabolism as evidenced by a decrease in sleeping times in animals acutely challenged with pentobarbital [16]. The absence of a change in the behavioral effects of 2.0 mg/kg methadone and 16 mg/kg pentobarbital over the course of the present study suggests an alteration in biotransformation or development of tolerance after weekly injections was not a factor in the results obtained here. Moreover, it is not clear how an interpretation based on metabolic interaction would account for key pecking rates which were higher after the combination than after either drug alone.

Responding in individual components of chained fixed-interval reinforcement schedules comes under the control of the temporal location of the component with respect to primary reinforcement [11]; response rate increases from component to component to primary reinforcement. Although the stimuli associated with the components of a chained schedule have generally been considered conditioned reinforcers, Gollub [11] suggested that the initial stimulus in an extended chain schedule may have aversive properties controlling very low rates of responding. The finding that pentobarbital increased key pecking rates in the initial chain component suggests pentobarbital ameliorated the suppressive effect of the initial chain stimulus. Barbiturates reliably increase responding suppressed by punishment or conditioned suppression procedures [2, 4, 9, 19, 22]. Whether this effect is due simply to the tendency for barbiturates to increase low response rates [24,25] remains unclear. Pentobarbital increased low rates of both punished and unpunished responding, but the extent of the increase depended on both the control response rate and whether or not punishment was involved [19]. When local rates of responding were equated under a two-component FR schedule of food presentation in which responding on one component was suppressed by delivery of pressurized air or electric shock after each response, pentobarbital increased punished and unpunished responding to about the same degree [27].

In contrast to pentobarbital's effect in the initial chain stimulus, methadone increased pausing in the first FI 30 sec component. Morphine decreases punished responding [14,28], a finding that may have bearing here. McGuire and Thompson's data [18] suggest that key pecking after methadone administration was not maintained by the weak conditioned reinforcing properties of onset of the second chain stimulus. Key pecking maintained by strong conditioned reinforcers, paired brief stimuli, is resistant to the effects of methadone [18]. Pausing in the initial component of the chained schedule was decreased by the concomitant administration of pentobarbital and methadone. Pentobarbital's ability to ameliorate the suppressive effect of the initial chain stimulus appeared to attenuate the rate-reducing effect of 0.50 and 1.0 mg/kg methadone in the initial FI component.

Although pentobarbital ameliorated the increased pausing produced by methadone, this effect is small when compared with the effect of pentobarbital on running response rate. The combination of pentobarbital and low doses of methadone increased running response rates more than methadone or pentobarbital alone. Synergistic effects of pentobarbital in combination with other drugs have been reported; however, the second drug has typically been a central nervous system stimulant [1, 29, 31]. Key pecking rates under the FI component of a mult FI FR food reinforcement schedule were increased by both methamphetamine and pentobarbital alone, with the combination producing increases that were greater than those obtained with the individual drugs [23].

Although additional research is necessary to determine how the stimulus functions operating under chained schedules may alter the nature of a drug interaction, effects of pentobarbital and methadone on key pecking maintained by chained fixed-interval schedules appear to involve two behavioral mechanisms. Performance in the initial component appears to be regulated by punishing properties of the stimulus correlated with that component. Pentobarbital and methadone have opposing behavioral properties in that methadone increases, while pentobarbital ameliorates the suppressing effects of that stimulus. Alternatively, or in addition, pentobarbital increases the low response rates via a rate-dependency effect. Performance in the terminal component is apparently regulated by the conditioned reinforcing and/or discriminative properties of the stimulus correlated with that component. Methadone and pentobarbital have additive effects, increasing the effectiveness of the prevailing stimulus mechanisms.

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