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Effects of Mephenytoin and Methsuximide on the Reaction Time of Pigeons

ELBERT BLAKELY, STEPHEN STARIN AND ALAN POLING

Department of Psychology, Western Michigan University, Kalamazoo, MI 49008

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BLAKELY, E., S. STARIN AND A. POLING. *Effects of mephenytoin and methsuximide on the reaction time of pigeons.* PHARMACOL BIOCHEM BEHAV 31(4) 787–790, 1988.—Although antiepilepsy drugs are used clinically, their behavioral effects are poorly understood. The present study examined the effects of mephenytoin and methsuximide, two antiepilepsy medications, on the reaction times of pigeons. Pigeons were trained to depress and hold a foot treadle until a stimulus change occurred. Releases within 2 sec of the stimulus change were reinforced with access to mixed grain; premature releases or releases occurring after the 2-sec limited hold were not reinforced. Mephenytoin (40, 60, 80, 120, and 160 mg/kg) and methsuximide (25, 50, 75, and 100 mg/kg) produced generally dose-dependent increases in median reaction times and decreases in percent responses that were reinforced. The present procedure has not previously been used with pigeons and is a promising technique for the study of reaction time with this species.

Mephenytoin Methsuximide Reaction time Pigeons Antiepilepsy Drugs

THE treatment of epilepsy, a condition afflicting 0.3% to 0.6% of the population (5), relies heavily on the use of drugs (14). To provide optimal treatment, the side effects of such drugs must be considered. Although the physiological effects of antiepilepsy medications are well-documented (19), their behavioral actions are less clear. The results of human research are equivocal and, moreover, the investigations have often been methodologically flawed due to ethical constraints (4). In an effort to conduct more carefully controlled studies, researchers have begun to examine the behavioral effects of antiepilepsy drugs in nonhumans (7,12). Several procedures have been used in these studies to profile drug effects on many learned and unlearned behaviors (12).

Little is known, however, about the effects of antiepilepsy drugs on reaction time. Lukas *et al.* (8) studied the effects of diazepam, a drug used for managing status epilepticus (15), and reported dose-dependent elevations in the reaction time of baboons. Diazepam also increased reaction time under a delayed matching-to-sample procedure with monkeys (11). The effects of other antiepilepsy drugs on reaction time have not been reported. One purpose of the present study was to investigate the effects on reaction time of mephenytoin (5-ethyl-3-methyl-5-phenylhydantoin), a hydantoin similar to phenytoin, and methsuximide (N,2-dimethyl-2-phenylsuccinimide), a succinimide similar to ethosuximide. Hydantoins and succinimides are frequently used to manage seizures; an investigation of their effects on reaction time would therefore be of interest. A second purpose was to determine whether reaction time as measured in the present study was sensitive to drug effects. The behavioral procedures employed in the present study apparently have not been used with pigeons, but similar methods have been used effectively to test reaction times with primates (10) and rodents (17).

METHOD

Subjects

Four drug-naive White Carneaux pigeons, all with brief histories of treadle-pressing, served as subjects. Birds were maintained at approximately 80% of their free-feeding weights, and were individually housed with unlimited access to water and grit.

Apparatus

Sessions were conducted in chambers measuring 38 cm high, 30 cm wide, and 40 cm long. A 6×6 cm aperture, centered on the front wall 8 cm from the floor, permitted feeding from a grain hopper. When operated, the hopper was illuminated with a 7-W light bulb. An 8×8 cm Plexiglas foot treadle was mounted on the front wall 7 cm from the right corner of the wall and 2 cm from the floor. The top of the treadle was covered with a coarse, high-friction material. When a force of at least 0.5 N was applied to the treadle, a microswitch was operated. A 1.5×1.5 cm Plexiglas window was installed 12 cm above the treadle, and red and white light bulbs (7-W) mounted behind the window served as stimulus lights. Illumination was provided by a 7-W houselight centrally located on the ceiling of each chamber. Ambient noise and ventilation were provided by a white noise generator (Grason-Stadler, Inc.) and by exhaust fans, respectively. Data collection and experimental events were controlled by a PDP8-E minicomputer (Digital Equipment Corporation, Maynard, MA) equipped with electromechanical interfacing

and SUPERSKED software (State Systems, Inc., Kalamazoo, MI).

Behavioral Procedure

Subjects were trained to depress the treadle when the white stimulus light was illuminated and release it when the light turned red, which occurred after a variable duration of time (i.e., the foreperiod). The mean foreperiod was 1.75 sec, and the individual durations were 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 sec. The foreperiod on a given trial was randomly selected from the distribution. Longer foreperiods were not used because pilot data suggested many birds were unable to reliably depress the treadle for substantially longer periods. When depressed, the treadle did not contact the chamber floor. Thus, much of the bird's weight was supported by the other foot, and some subjects in pilot work were unable to maintain this position for long periods of time. Moreover, the 3-sec maximum is generally consistent with that used in other reaction time research with rats and monkeys (9).

Correct releases, those within a 2-sec limited hold after the foreperiod elapsed, produced 3-sec access to grain. If a release occurred before the foreperiod elapsed (i.e., a premature release), the stimulus light was extinguished, grain was not presented, and the same foreperiod duration was reprogrammed for the next trial. The foreperiod was recycled to ensure that subjects could not obtain frequent reinforcement by merely depressing the treadle for a fixed amount of time. If a release occurred after the 2-sec limited hold, grain was not presented, and a new foreperiod was programmed for the upcoming trial. A 5-sec intertrial interval (ITI) followed access to grain and incorrect releases. Treadle presses during the ITI extinguished the houselight until the treadle was released, at which time the ITI began anew. Each daily session ended after 40 grain deliveries, 45 minutes, or 100 trials, whichever came first.

Pharmacological Procedure

Birds were exposed to the reaction time procedure until each met the criterion for food delivery on at least an average of 70% of the trials and there was no visually evident trend in median reaction time and percent reinforced trials across 5 consecutive sessions. This criterion was reached after 44, 32, 46, and 48 sessions for P1, P2, P3, and P4, respectively. Methsuximide and mephenytoin were then tested. Four doses of methsuximide (25, 50, 75, and 100 mg/kg) and vehicle injections were given intramuscularly (IM) 30 min prior to test sessions. The drug was dissolved in a vehicle of 80% propylene glycol and 20% ethyl alcohol. Five doses of mephenytoin (40, 60, 80, 120 and 160 mg/kg) and vehicle injections were given IM 8 hours prior to test sessions. Vehicle was dimethyl sulfoxide (DMSO). Presession injection intervals were those at which peak effects occurred in pilot testing. All injections were administered at a 1 ml/kg injection volume. Both drugs were tested acutely under a BBCDBBCD regimen where B, C, and D represent baseline, vehicle control, and drug sessions respectively. All birds received 2 determinations at each dose; doses were given in an irregular order that differed for each bird. Two birds received methsuximide first (P2, P4); the other two (P1, P3), mephenytoin first.

RESULTS

Mephenytoin

The upper panels of Fig. 1 depict the reaction times of pigeons during control and mephenytoin sessions. A reaction time was defined as the elapsed time from the change in color of the stimulus light to the release of the treadle. Thus, the medians were computed using the reaction times on reinforced trials and on trials in which releases occurred after the 2-sec limited hold. Premature releases, which occurred before the stimulus light turned red, did not yield reaction times and thus did not figure into the medians. Note that the ordinate is scaled in logarithmic units and data are presented separately for the first and second exposure to each dose. Control data points represent the means of five sessions (one control session prior to each of five doses of mephenytoin). Drug data points represent the median reaction time during a single session. For all subjects, mephenytoin increased median reaction time in a generally dose-dependent fashion. In addition, even the lower doses of mephenytoin increased reaction time, suggesting that the measure is a sensitive assay of drug effects. For P1, P3, and P4, the effects on the first determination were often larger than those on the second determination.

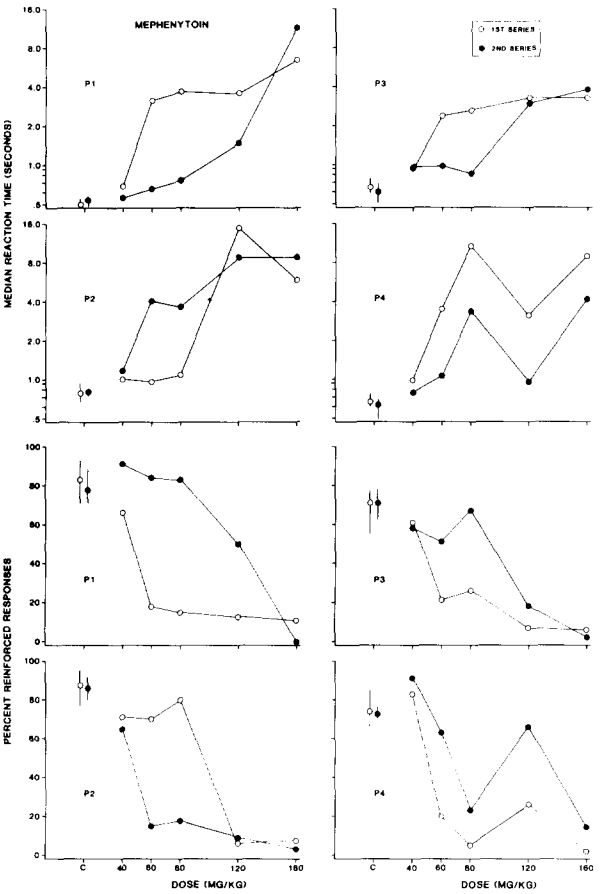

FIG. 1. Effects of mephenytoin on the median reaction time and percent of responses reinforced for individual pigeons. Drug data are presented separately for each of two series of administrations. Control data (C) represent the mean of five control sessions immediately before the drug sessions in each series. Vertical lines through control data points represent the range across these sessions.

The lower panels of Fig. 1 show the percent of responses that met the criterion for reinforcement during control and drug sessions. These data represent trials on which the treadle was released within the 2-sec limited hold after the

TABLE 1

THE PERCENT OF TRIALS IN WHICH PREMATURE RELEASES OCCURRED DURING CONTROL (C) AND MEPHENYTOIN SESSIONS

Subject	C	40	60	80	120	160
			Mephenytoin (1st determination)			
P1	16	8	18	12	4	14
P2	7	7	16	10	10	9
P3	18	6	10	3	4	5
P4	25	10	8	7	13	2
			Mephenytoin (2nd determination)			
P1	20	5	13	4	6	5
P2	9	5	9	7	3	19
P3	21	12	14	18	2	1
P4	25	9	8	9	11	6

foreperiod elapsed; thus, trials on which the criterion for reinforcement was not met included premature releases and releases after the 2-sec limited hold. Mephenytoin generally resulted in dose-dependent decreases in the percent of reinforced responses. Again, the drug had greater effects in the first determination than in the second for P1, P3, and P4. Table 1 shows for each pigeon the percent of trials on which premature releases occurred in control sessions and mephenytoin sessions. The percentage of premature releases was either unaffected or decreased by drug administrations.

Methsuximide

The upper panels of Fig. 2 show the median reaction times during control and methsuximide sessions. Control data points represent the means of four sessions. Drug data were collected and plotted in the same way as for mephenytoin. In 3 of 4 subjects, methsuximide produced generally dose-dependent increases in median reaction times. For these three subjects, methsuximide usually increased reaction time at even the lowest dose.

The percent of responses that met the criterion for reinforcement is shown in the bottom panels of Fig. 2. In three of the four subjects, methsuximide also decreased percent reinforced responses. There seemed to be no consistent differences in the two determinations for either reaction time or percent of responses that were reinforced. Table 2 shows for each pigeon the percent of trials with premature releases. These data show no consistent drug effects. At some doses, no effect was obtained; at others, increases or decreases were observed.

DISCUSSION

The procedures employed in the present study provided a workable assay of reaction time in pigeons. Moreover, reaction time as assayed with these procedures was sensitive to drug effects. In general, acute administrations of mephenytoin produced dose-dependent increases in reaction time and decreases in percent responses that met the criterion for reinforcement. The effects for P1, P3, and P4 decreased in the second determination, suggesting that tolerance developed in these subjects. The decreases in percent responses that met the criterion for reinforcement resulted from increases in trials with reaction times beyond the 2-sec limited

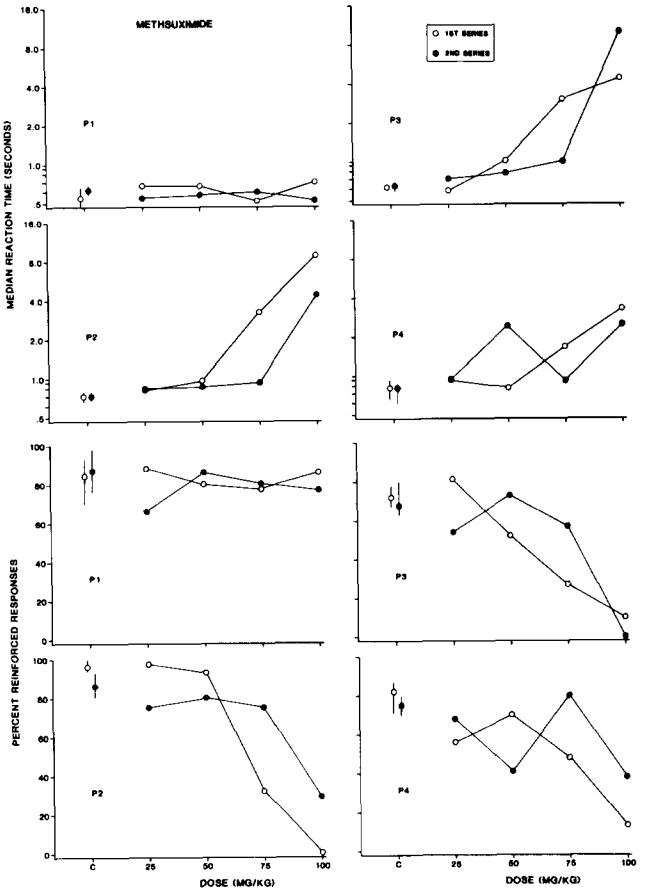

FIG. 2. Effects of methsuximide on median reaction time and percent responses reinforced for individual pigeons. Drug data are presented separately from each of two administrations. Control data (C) represent the mean of four control sessions immediately prior to drug sessions in each series. Vertical lines represent the range of control data across these sessions.

TABLE 2

THE PERCENT OF TRIALS IN WHICH PREMATURE RELEASES OCCURRED DURING CONTROL (C) AND METHSUXIMIDE SESSIONS

Subject	C	25	50	75	100
			Methsuximide (1st determination)		
P1	15	4	16	14	4
P2	5	0	5	3	25
P3	13	8	8	3	6
P4	12	15	23	9	10
			Methsuximide (2nd determination)		
P1	9	30	13	16	17
P2	8	8	6	8	8
P3	18	11	9	4	19
P4	18	19	4	10	6

hold rather than in premature releases. As evidence, the percent of trials with premature releases was unaffected or decreased during drug sessions.

Administrations of methsuximide generally produced dose-dependent increases in reaction time and decreases in percent responses that met criterion for reinforcement. The latter resulted primarily from increases in reaction times beyond the 2-sec limited hold, as percent of trials with premature releases was not consistently affected by methsuximide. Unlike mephenytoin, there was no consistent difference between the two determinations. Moreover, methsuximide often produced smaller effects than mephenytoin, particularly at the lower doses. One subject, P1, was unaffected by administrations of methsuximide. This subject was also tested with higher doses (150 and 200 mg/kg), both of which had no effect. The reasons for this insensitivity are unknown. It is possible that for this bird the onset of drug effects was delayed such that the 30-min presession injection time was too brief. Or because this bird received methsuximide after mephenytoin, perhaps tolerance developed.

It is unclear the extent to which the present results apply to the clinical use of mephenytoin and methsuximide. The doses were higher than those used to manage seizures in humans (3), but the metabolism of pigeons differs considerably from that of humans. Also the capacity of the doses in the present study to block seizures in pigeons is unknown. Thus, extrapolations to humans await further research.

Although relatively little is known about the behavioral effects of mephenytoin and methsuximide in nonhumans, a previous investigation (2) found that acute administrations of these drugs increased errors and reduced response rates in pigeons responding under a repeated acquisition procedure. These effects were generally dose-dependent, and the lowest doses at which they were observed were similar to the minimal doses that disrupted performance in the present study. Performance under the repeated acquisition procedure is very sensitive to drugs from several classes (18). That the reaction time assay employed in the present study was comparably sensitive to the effects of mephenytoin and methsuximide is therefore of interest.

The methodology in previous studies of reaction time using pigeons (6, 13, 16) has two potential weaknesses. First, no preparatory response was required; a discriminative stimulus was simply presented after an ITI and the time to respond was recorded. With this kind of procedure, there is no guarantee that the subject attends to the stimulus, or is in a position to respond when it appears. Second, key-pecking was the instrumental response in these studies. Because a change from conditions correlated with a low probability of reinforcement to those with a greater probability of reinforcement has been shown to elicit key-pecking in pigeons (1), reaction times were perhaps contaminated by variables controlling elicited pecking. In the present study, subjects were required to emit a preparatory response, the nature of which maximized the probability of contact with the signal to respond and ensured the possibility of prompt responding. The present procedure also used foot-treadling to obviate unwanted influences by elicited pecking. This technique appears to be a promising method for studying drug effects on reaction times using pigeons as subjects.

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