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Acute and Chronic Effects of Phenytoin on Fixed-Ratio Performance of Pigeons

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KRAFFT, K. AND A. POLING. *Acute and chronic effects of phenytoin on fixed-ratio performance of pigeons.* PHARMAC. BIOCHEM. BEHAV. **16**(5) 843–846, 1982.—The effects of phenytoin on the key-pecking of pigeons maintained under a fixed-ratio 50 schedule of food reinforcement were studied. When initially administered across a range of presession intervals, acute intramuscular injections of 10 and 20 mg/kg of the drug generally decreased response rates. The magnitude of this effect was greater at the larger dose. Comparison of the effects of 10 and 20 mg/kg doses before and after chronic exposure to phenytoin showed that a degree of tolerance to the drug's behavioral effects did develop.

Phenytoin Key-pecking Fixed-ratio schedule Anticonvulsant drugs Tolerance Pigeons

PHENYTOIN (Dilantin) was introduced in 1938 for the treatment of epilepsy. Its development resulted from a systematic attempt to find a drug capable of suppressing convulsions in laboratory animals. Phenytoin did so, and also proved effective in controlling certain forms of epilepsy in humans [6, 9, 11]. Beyond being effective, phenytoin did not cause the heavy sedation associated with bromide and barbiturates, which it soon replaced as the antiepileptic of choice.

While many studies have examined the anticonvulsant properties of phenytoin, as well as the drug's several undesirable side effects, among them dizziness, gingival hyperplasia, peripheral neuropathy, hyperglycemia, blurred vision, and hirsutism [6, 9, 11], nothing is known concerning its effects on schedule-controlled responding. A recent investigation [1] found that phenytoin impaired the matching-to-sample performance of mentally retarded humans, but other studies in this vein have not appeared. This is surprising, for other anticonvulsants, the barbiturates in particular, have been studied carefully with respect to their effects on operant performance [7]. Under a variety of schedules, including those which engender relatively high rates of responding (e.g., fixed-ratio), barbiturates typically increase response rates at low-to-moderate doses, and decrease responding at high doses [2, 4, 5, 7, 10]. It is not clear whether phenytoin produces similar effects.

The present study explored the acute, chronic, and post-chronic effects of two doses of phenytoin on the key-pecking of pigeons maintained under a fixed-ratio 50 schedule of food reinforcement.

METHOD

Subjects

Three individually housed White Carneaux pigeons, maintained at 80% of free-feeding weights, served as subjects. All subjects had previous experience under a variable-interval schedule of food delivery.

Apparatus

Responding was studied in a 38-cm high, 30-cm wide, and 40-cm long chamber. A 5-cm by 5-cm opening horizontally centered in the work panel 8 cm above the floor of the chamber allowed access to Purina pigeon grain. Two response keys, 2.5 cm in diameter, were symetrically located on the work panel, 12 cm from the adjacent wall and 24 cm above the chamber floor. The left key was illuminated with white light, the right key remained dark and inoperative throughout the study. Operation of the left key required a force of approximately 0.08 Newton. Ambient chamber illumination was provided by two clear 7 W bulbs centered above the transparent ceiling of the chamber. Continuous white noise masked extraneous sounds. Electromechanical equipment was used to program events and record responses.

Procedure

Training. Key-peck responding was initially maintained under a fixed-ratio 1 (FR 1) schedule of food reinforcement (where each response was followed by 4 sec of grain delivery), which was gradually increased over the next 10 sessions to a FR 50. This schedule was in effect for the remainder of the experiment. Sessions were 30 min in duration and typically occurred six days a week at about the same time each day.

Initial acute regimen. After the responding of individual birds stabilized under the FR 50 schedule, an injection regimen was begun in which each bird received an intramuscular injection of 1.0 ml/kg isotonic saline solution, or phenytoin. Stable responding was defined as the mean response rate at which responding during sessions N and N−1 was within ±5% of the mean response rate during sessions N−1 and N−2, when N is the most recent session. Phenytoin was prepared as a commercially available injection (Parke-Davis, Morris Plains, NJ) diluted with isotonic saline solution to an injection volume of 1.0 ml/kg. Each bird received a single

administration of 20 mg/kg phenytoin at presession intervals of 15, 45, and 90 min, and two administrations of 10 mg/kg at presession intervals at 15, 45, 90, and 180 min. Drug sessions occurred approximately once a week and each drug administration was preceded by at least three consecutive control (saline) sessions during which responding was stable as defined above. Doses and presession intervals were arranged in an irregular order that differed across subjects.

Chronic regimen. Following completion of the acute drug regimen, each bird received a minimum of five saline sessions prior to chronic drug administration. Once stability was obtained during saline sessions, 10 mg/kg of phenytoin was administered 15 min prior to each of 20 sessions; birds were injected seven days a week during this period. Saline injections were then reinstated for six sessions followed by the chronic administration of 20 mg/kg phenytoin 15 min prior to each of 15 consecutive sessions.

Acute replication. Following the chronic regimen, the effects of 10 and 20 mg/kg doses of phenytoin administered acutely 15 min prior to the session were again determined. Five saline sessions occurred prior to the replication of the acute regimen. Each dose was given a single time to each subject during this second acute regimen; procedures were otherwise identical to those described for the intial acute regimen.

RESULTS

Figure 1 shows the effects of phenytoin when initially administered acutely. This figure presents the mean response rate of each bird during control and drug sessions at each presession injection interval. The mean response rates during control sessions remained stable throughout this phase of the study. In general, phenytoin at 10 mg/kg decreased response rates for all birds at each presession injection interval, although the greatest decreases in rate occurred at the 45 min interval, and response rates approached control values when the drug was given 90 or 180 min prior to the session. At all injection intervals, responding of each bird was almost completely suppressed at the 20 mg/kg dose. Nonsystematic observations failed to indicate drug-induced changes in overt behavior; gross motor incapacitation seemingly was not responsible for the rate-decreasing effects of phenytoin.

Figure 2 shows mean response rates for blocks of five sessions prior to and during the chronic drug regimen. For two birds (S1 and S2), responding was reduced by 10 mg/kg for 20 sessions; responding of the other bird (S3) was little affected by this dose. Control response rates of all subjects returned to pre-drug levels following the initial (10 mg/kg) chronic drug regimen. Chronic exposure to the 20 mg/kg dose immediately reduced the response rates of all birds; this effect diminished by the final block of five sessions in one subject (S1) only.

Comparison of response rates during acute exposure to phenytoin before and after chronic drug administration shows that a degree of tolerance did develop to the drug. These data are presented in Table 1, which clearly shows that for all birds phenytoin at 10 and 20 mg/kg decreased responding less during the second acute exposure than during the first. Note that in this table mean control and drug rates for the initial acute regimen are identical to those presented in Fig. 1 (15 min presession injection interval), while tabled data for the acute replication do not appear elsewhere,

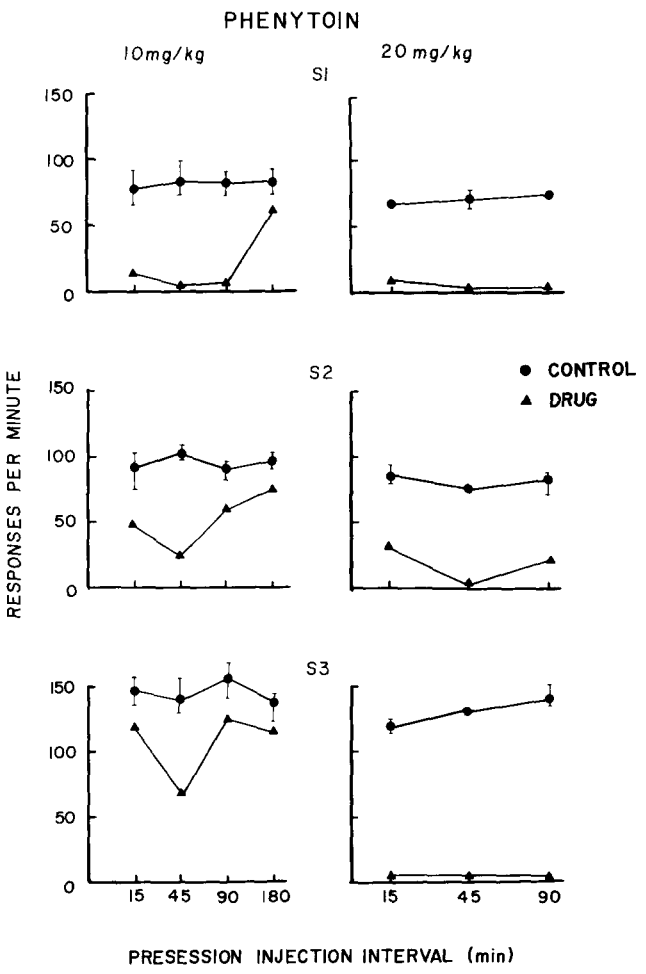

FIg. 1. The effects of phenytoin on FR performance across presession injection intervals. The control data are expressed as the mean response rate for the three sessions prior to each drug administration. The vertical lines indicate the standard error of the mean.

although these control values are relatively close to those presented in Fig. 2.

DISCUSSION

The present findings indicate that phenytoin administered acutely at doses of 10 and 20 mg/kg decreased pigeons' responding under a FR 50 schedule of food delivery. This effect was dose-dependent; greater decrements in response rates occurred at the larger dose. Phenytoin's actions were evident across the range of presession injection intervals examined (15–180 min). At the lower (10 mg/kg) dose, the magnitude of the rate decreases associated with the drug increased as the presession injection interval was raised from 15 to 45 min, then decreased at intervals of 90 and 180 min.

Other reports of the effects of phenytoin on schedule-controlled responding are lacking, although it has been found that the drug interferes with humans' operant responding in a matching-to-sample task [1]. Barbiturates, which possess anticonvulsant properties (phenobarbital is a common

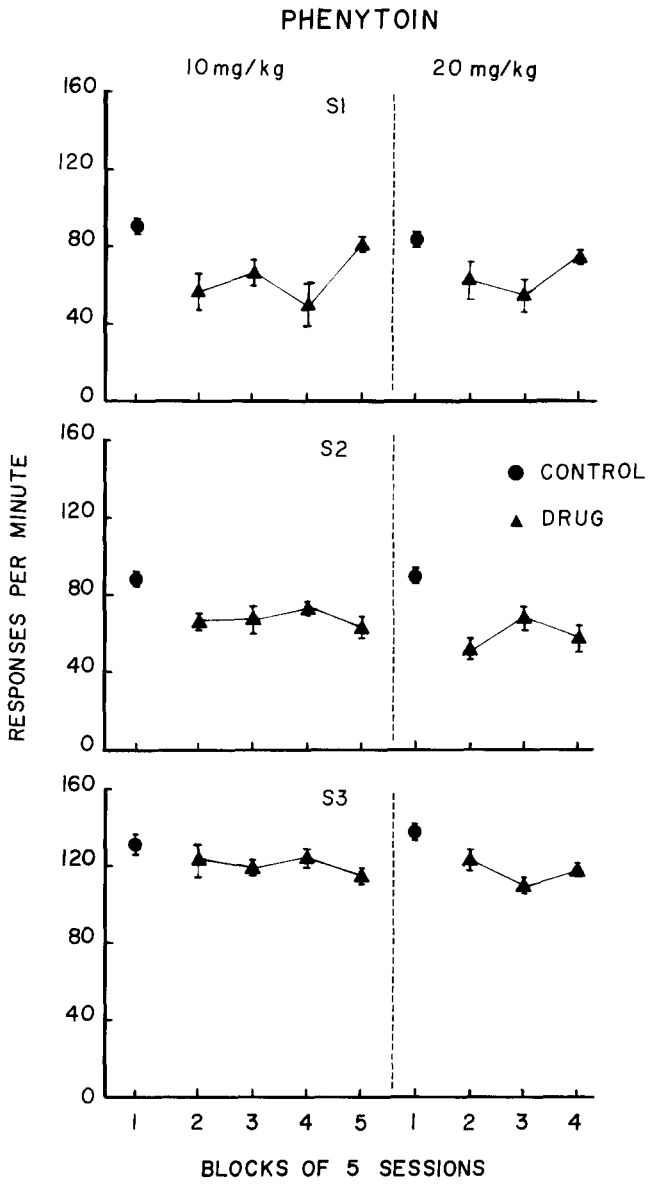

FIG. 2. The mean response rate for each subject during saline and chronic phenytoin administration. The control data represent the mean of three sessions prior to drug administration; each drug data point represents the mean of five consecutive sessions. The vertical lines indicate the standard error of the mean.

antiepileptic) and structurally resemble phenytoin, have, however, been studied carefully with respect to their effects on schedule-controlled responding. In general, the various barbiturates produce similar behavioral effects, differing primarily in potency and duration of action. With respect to

TABLE 1

THE EFFECTS OF PHENYTOIN GIVEN ACUTELY PRIOR TO (INITIAL ACUTE REGIMEN) AND FOLLOWING (ACUTE REPLICATION) CHRONIC DRUG ADMINISTRATION

	Responses per Minute			
Subject	Control	10 mg/kg	Control	20 mg/kg
	Initial Acute Regimen			
S1	75 (61– 90)	14	64 (63– 65)	15
S2	91 (80–105)	49	86 (82– 93)	31
S3	146 (137–157)	120	118 (114–121)	0.2
	Acute Replication			
S1	83 (77– 87)	75	81 (76– 84)	45
S2	78 (73– 82)	62	93 (86– 96)	87
S3	113 (109–115)	118	114 (112–115)	70

Responding was maintained under a FR 50 schedule of food reinforcement and drug was given 15 min prior to the session. The control rates are the mean of the three saline sessions that immediately preceded drug administrations. Values in parentheses represent the range of response rates across these control sessions.

FR performance, low-to-moderate doses of these drugs typically increase response rates in pigeons and other species, while high doses reduce responding (e.g., [2, 4, 5, 7, 10]. Such effects were not observed with phenytoin in the present study, where response rate increases did not occur.

Clinical investigations have found that tolerance does not develop to the therapeutic (anticonvulsant) action of phenytoin, but may develop to certain undesirable side effects, such as dizziness [6]. Tolerance refers in general to diminished responsiveness to a drug with repeated exposure, and can be demonstrated by showing that the dose-response curve shifts to the right during or after chronic exposure or, alternately, by showing that the effects of a given dose lessen across administrations [3,8]. In the present study, the effects of phenytoin given acutely did diminish substantially after chronic exposure to the drug, which is indicative of tolerance. Further, in the case of S1, the rate reduction produced by phenytoin decreased over the course of chronic exposure, suggesting the development of tolerance in this bird. Similar effects may have been observed in the other birds had the chronic regimen been extended, but this possibility was not explored.

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