*Pharmacology Biochemistry & Behavior*, Vol. 31, pp. 233–237. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

BRIEF COMMUNICATION

# Effects of Mephenytoin on Schedule-Controlled Responding in the Pigeon

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PELLETTIERE, V., D. DELANEY, H. SCHLINGER AND A. POLING. *Effects of mephenytoin on schedule-controlled responding in the pigeon.* PHARMACOL BIOCHEM BEHAV 31(1) 233–237, 1988.—Acute and chronic effects of mephenytoin (30–360 mg/kg) were examined in pigeons responding under a multiple fixed-ratio 50 fixed-interval 90-sec schedule of food delivery. The highest dose administered acutely (240 mg/kg) produced substantial reductions in rate of responding under both components of the multiple schedule; the effects of other doses were small and inconsistent. With chronic exposure tolerance appeared to develop to the rate-decreasing effects of the drug.

Mephenytoin Pigeons Multiple schedule Fixed-ratio schedule Fixed-interval schedule

DRUGS from several chemical classes are used in the clinical management of epilepsy. Interestingly, drugs from the same chemical class sometimes differ with respect to their toxic physiological effects. For example, phenytoin, a hydantoin, can produce untoward side effects including gingival hypertrophy, hirsutism, and gastrointestinal symptoms. It is nonetheless a popular drug for treating all types of epilepsy except absence seizures (16). Another hydantoin, mephenytoin, is similar to phenytoin in antiepileptic spectrum. It may cause less ataxia, gingival hyperplasia, gastric distress, and hirsutism than phenytoin (16), which has led some researchers to suggest the use of mephenytoin as an alternative to phenytoin (4). Serious adverse side reactions (e.g., morbilliform rash, fever, lymphadonaphy, aplastic anemia, leukopenia, hepatoxicity, periartheritis nodosa, and lupus erythematosus) are, however, relatively common with mephenytoin. Use of the drug therefore is largely restricted to patients who fail to respond favorably to alternative medications (16).

Phenytoin and mephenytoin differ with respect to toxic physiological side effects; they may also differ with respect to behavioral actions. No comparison of the behavioral effects of phenytoin and mephenytoin in humans has appeared. Although phenytoin has been studied rather extensively in nonhumans [for reviews see (8,13)], researchers have only recently begun to investigate the behavioral effects of mephenytoin (2,17). These studies permit some comparisons between the two drugs. For example, in pigeons responding under a repeated acquisition procedure and under a fixed-consecutive-number schedule, both drugs decrease response rates and increase errors at moderate and high doses (2, 9, 11, 14, 17).

The behavioral effects of mephenytoin on schedule-controlled behavior have not been reported. Phenytoin has been shown to reduce relatively high response rates in pigeons maintained by a fixed-ratio 50 schedule of reinforcement (6). It has also been shown to reduce high rates of responding in rats at doses that do not systematically affect low response rates (7,12). The purpose of the present study was to examine the effects of acute and chronic administrations of mephenytoin on schedule-controlled behavior in pigeons.

## METHOD

### *Subjects and Apparatus*

Three experimentally-naive White Carneaux pigeons,

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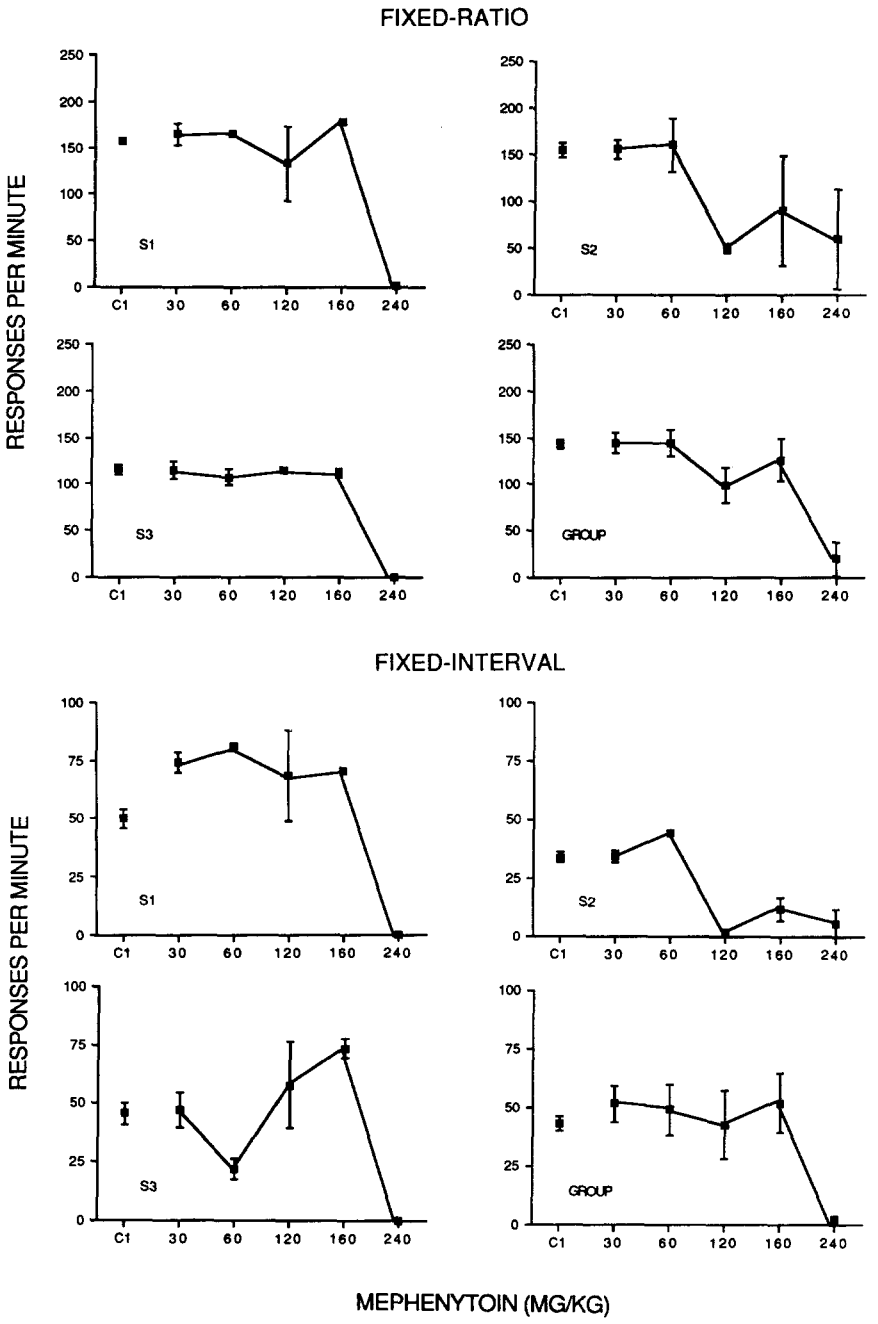


FIG. 1. Response rates for individual pigeons and for the subjects as a group under the FR 50 (upper panels) and FI 90-sec (lower panels) components during the acute phase of the study. Data at C1 indicate mean response rates across all control sessions immediately prior to acute drug administrations; vertical lines represent the standard error. Acute drug data for each bird indicate performance across two determinations at the dose listed.

maintained at approximately 80% of their free-feeding weight, served as subjects. Subjects were individually housed with unlimited access to grit and water. They were tested in three computer-controlled operant conditioning chambers described in detail elsewhere (13). Each chamber contained a food hopper and three response keys; only the center key was lighted and operative in this study.

*Behavioral Procedure*

Following initial keypeck training, subjects were exposed to a multiple fixed-ratio 1 fixed-interval 1-sec (mult FR 1 FI 1-sec) schedule of food delivery. The value of each component was gradually increased over 20 sessions to a mult FR 50 FI 90-sec. This schedule was employed for the duration of

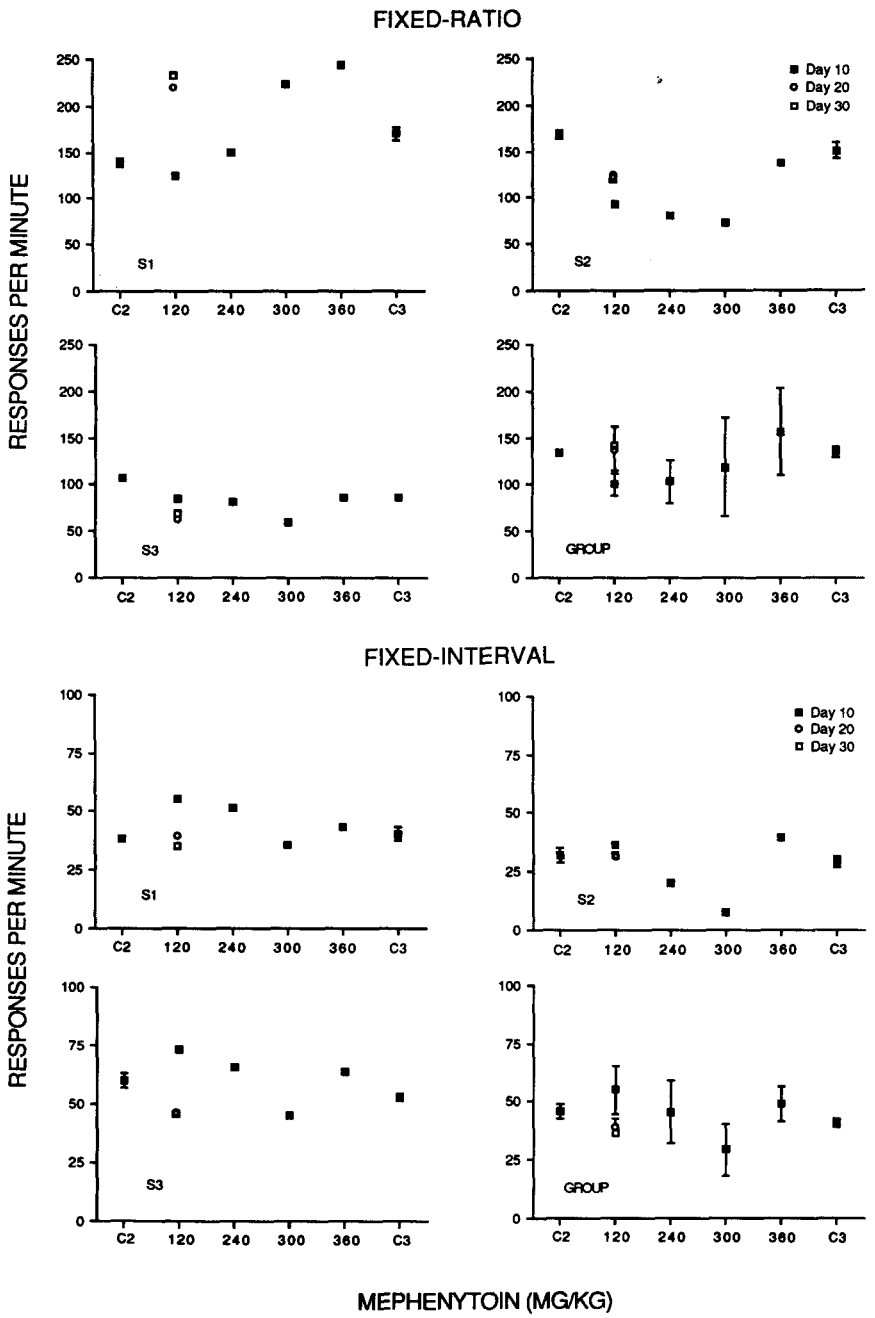


FIG. 2. Response rates for individual pigeons and for the subjects as a group under the FR 50 (upper panels) and FI 90-sec (lower panels) components during the chronic phase of the study. Data at C2 indicate mean response rates during all control sessions prior to chronic drug administrations. Data at C3 indicate mean response rates during all baseline (no injection) sessions following chronic drug exposure. During the chronic phase, 120 mg/kg mephenytoin was administered daily except when challenge doses (240, 300, 360 mg/kg) were given; data are presented for the tenth, twentieth, and thirtieth day of exposure to 120 mg/kg. Each challenge dose was given to each bird on a single occasion. Vertical lines represent standard errors.

the experiment. The center key was illuminated red during the FR components and blue-green during the FI components; the color of key illumination alternated at 5-min intervals. The 50th keypeck under the FR schedule and the first keypeck emitted at least 90-sec after blue-green key illumination or food delivery under the FI schedule produced 3-sec

access to mixed grain. Sessions were 30 min in duration and were conducted seven days a week at approximately the same time each day.

*Pharmacological Procedure*

Subjects were exposed to the mult FR 50 FI 90-sec schedule until the response rates of the individual subjects were stable under both components. The criterion for stability was three consecutive sessions in which the response rate in each individual session was within 10% of the mean rate of responding across those three sessions. When this criterion was met, acute dose-response determinations were begun. Five doses of mephenytoin (30, 60, 120, 160, and 240 mg/kg), obtained from Sandoz (East Hanover, NJ) and dissolved in dimethyl sulfoxide (DMSO), were evaluated. In all phases of the study, drug (and control) injections were administered intramuscularly (IM) at an injection volume of 1 ml/kg. Drug doses and the presession injection interval were selected on the basis of those used in previous investigations (1, 2, 17). During acute dose-response determinations, each bird received all doses on two occasions. Doses were given in a random order. All drug administrations were separated by at least three sessions in which responding was stable as defined above; one of these sessions was preceded by a control injection. The control injections consisted of isotonic saline solution; prior data (2) indicate that DMSO is not behaviorally active at the volume used in this study.

Following completion of the acute dose-response determination, all birds received control injections prior to at least five consecutive sessions. Subjects then received 120 mg/kg mephenytoin prior to each of ten consecutive sessions. This dose was the lowest one that decreased any subject's response rate under either component of the mult schedule when given acutely. Following the tenth day of chronic exposure, subjects were injected with a challenge dose of 240 mg/kg. Thereafter, challenge doses of 300 and 360 mg/kg were administered with ten days of chronic injections of 120 mg/kg between each dose. Challenge doses were given in ascending order because of possible toxic effects (e.g., death) at doses above 240 mg/kg; the effects of such doses in pigeons had not been previously reported or examined by us. Following the last challenge dose (360 mg/kg), no other injections were given and subjects were exposed to the mult schedule until responding stabilized.

## RESULTS

Figure 1 shows response rates for individual subjects and for subjects as a group during acute drug and control conditions. Although baseline rates were higher under the FR component, drug effects were similar under the FR and FI components. For two subjects, response rates were substantially reduced only at the 240 mg/kg dose of mephenytoin; rate reductions also were observed at 120 and 160 mg/kg for subject S2. Repeated measures analysis of variance (5) of acute group data revealed significant overall effects under both the FR, $F(5,30)=8.9$, $p<0.01$, and FI, $F(5,30)=3.76$, $p<0.05$, components. Planned comparisons by the protected least significant difference (LSD) method revealed that the mean group response rate at 240 mg/kg was significantly lower than the mean control rate under both the FR (LSD=5.33, $p<0.01$) and FI (LSD=2.97, $p<0.01$) components. Mean response rates at all other doses did not differ significantly from control ($p>0.05$).

Figure 2 shows response rates for individual subjects and for subjects as a group during pre- and postchronic control sessions, during the tenth, twentieth, and thirtieth sessions of chronic exposure to 120 mg/kg mephenytoin, and during exposure to the 240, 300, and 360 mg/kg challenge doses. Although considerable variability across subjects was evident during the chronic drug regimen, tolerance appeared to develop to the rate-reducing effects of mephenytoin. This is evident if the effects of 240 mg/kg are compared when that dose was given acutely and as a challenge dose. Correlated *t*-tests (5) revealed that the mean group response rate under both the FR, $t(2)=36.79$, $p<0.01$, and the FI, $t(2)=15.33$, $p<0.01$, components was significantly higher when 240 mg/kg was given as a challenge dose than when it was given acutely.

## DISCUSSION

Anticonvulsant drugs from several chemical classes, including succinimides, hydantoins, and barbiturates, are used widely and effectively in the treatment of epilepsy. Investigations with nonhumans, reviewed elsewhere (8,13), indicate that there often are qualitative and quantitative differences in the behavioral effects of drugs from different chemical classes. Moreover, recent evidence suggests that there frequently are differences in the behavioral effects of anticonvulsant drugs even when they belong to the same chemical class, that is, when they are structurally similar (2, 3, 9–11, 14, 17). Whether drugs from the same chemical class produce dissimilar behavioral effects may depend on the assay employed. For example, the succinimides ethosuximide and methsuximide have dissimilar effects under a repeated acquisition procedure and a fixed-consecutive-number schedule (2, 9, 10, 14, 17), but they produce comparable effects under a mult FR 50 FI 90-sec schedule (3,4).

Phenytoin and mephenytoin, both hydantoins, have previously been shown to produce similar effects under a repeated acquisition procedure where both drugs substantially increased errors and decreased rate of responding (2, 9, 14). Moreover, both drugs produced generally dose-dependent decreases in accuracy and rate of responding under a fixed-consecutive-number schedule (11,17). The present findings indicate that mephenytoin at a sufficiently high dose also reduces responding under both components of a mult FR 50 FI 90-sec schedule and that tolerance develops to this effect.

The effects of phenytoin under a mult FR 50 FI 90-sec have not been examined in pigeons. In rats responding under a mult FR 20 FI 60-sec schedule, acute administrations of phenytoin (20–50 mg/kg) at higher doses reduced response rates under both components (7). Chronic drug effects were not examined in that study, but tolerance to the rate-decreasing effects of phenytoin was observed in pigeons responding under simple FR schedules (6). When compared to those of the present study, these results suggest that phenytoin and mephenytoin produce qualitatively similar effects on schedule-controlled performance, as they do under other behavioral assays.

## ACKNOWLEDGEMENTS

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