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

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THE EFFECTS OF MEPHENYTOIN ON SCHEDULE-CONTROLLED RESPONDING IN THE PIGEON

by

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THE EFFECTS OF MEPHENYTOIN ON SCHEDULE-CONTROLLED RESPONDING IN THE PIGEON

Victoria Mary Pelletiere, M.A.
Western Michigan University, 1991

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. Tolerance appeared to develop to the rate-decreasing effects of mephenytoin following chronic exposure to the drug.
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Victoria Mary Pelletiere
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CHAPTER I

INTRODUCTION

According to Rall and Schleifer (1985), the term *epilepsies* refers to:

- a collective designation of a group of chronic central nervous system disorders having in common the occurrence of sudden and transitory episodes (seizures) of abnormal phenomena of motor (convulsions), sensory, autonomic, or psychic origin. The seizures are nearly always correlated with abnormal and excessive EEG discharges (p. 446).

Epilepsies have been classified into several types based on the clinical manifestations of the observed seizures and electroencephalograph (EEG) assessments of brain activity during the seizures. While the prevalence of each type of epilepsy differs, some form of epilepsy has been observed in three to six individuals per 1000 people in the general population (Hauser, 1978). The incidence of epilepsy is considerably higher among retarded individuals. It is estimated that 20% of severely impaired, institutionalized individuals exhibit epilepsy (Corbett, Harris, & Robinson, 1975).

The effects of uncontrolled seizures are well-documented. The loss of control for even a brief period of time may be life-threatening, depending upon what the person is doing at the time (Gibbs et al., 1982). Moreover, uncontrolled seizures may produce brain damage, and are associated with debilitating short- and long-term changes in behavior, including intellectual deterioration (Rall & Schleifer, 1985). Finally, the social ramifications of motor convulsions or inappropriate behavior may be detrimental to the individual. As such, the importance of treating epilepsy cannot be overstated.

Interventions based on the principles of respondent and operant conditioning have been employed in the treatment of epilepsy (for reviews, see Krafft & Poling,
1982b; and Mostofsky & Balaschak, 1977). Unfortunately, many of the investigations employing these procedures have had serious methodological flaws including weak experimental designs, inadequate quantification of the dependent measures, a lack of interobserver agreement, and questionable generality of the treatment effects (Gibbs et al., 1982; Krafft & Poling, 1982b). Although behavioral interventions may prove to be promising as adjuncts to pharmacological therapies, their efficacy as alternatives to chemotherapy has not yet been demonstrated. As such, pharmacological therapies remain the most effective and prominent treatment for epilepsy (Jones & Woodbury, 1982; Krafft & Poling, 1982b; Rall & Schleifer, 1985).

The overall goal of pharmacological treatments of epilepsy is to select the appropriate drug or combination of drugs that best controls the seizures in the individual at an acceptable level of side effects (Rall & Schleifer, 1985, p. 449). Six primary classes of drugs are currently used in the clinical management of epilepsy. These classes are: barbiturates, benzodiazepines, carbamazepine, hydantoins, succimides, and sodium valporate (Gibbs et al., 1982). From the turn of the century until the 1930s, phenobarbital, a barbiturate, was the drug of choice in the treatment of epilepsy. Phenytoin, a hydantoin, was introduced in the late 1930s and gradually replaced phenobarbital as the most commonly prescribed antiepileptic drug for all seizure types except absence seizures (Poling & Picker, 1987). Since that time, a number of structurally and chemically different drugs have been employed in the treatment of this disorder. Researchers have suggested that, in general, complete seizure control can be achieved with antiepileptic medications in up to 50% of patients and significant improvements can be expected in another 25% (Rall & Schleifer, 1985).
No one drug or combination of drugs has been effective in achieving complete control of any type of seizure. Moreover, drugs which achieve satisfactory control of one seizure type may be ineffective with other types of seizures. For example, phenobarbital and phenytoin, the principle agents used to treat generalized tonic-clonic seizures, are ineffective in controlling absence seizures. They may, in fact, increase their frequency (Rall & Schleifer, 1985). Similarly, ethosuximide, the drug of choice in the treatment of absence seizures, is generally ineffective in controlling complex partial seizures (Rall & Schleifer, 1985).

The selection of antiepileptic drugs is further complicated by the physiological and behavioral side effects produced by the various agents. Rall and Schleifer (1985) note that many of these drugs may not only fail to control seizures, but frequently cause side effects that range in severity from minimal impairment of the central nervous system (CNS) to death from aplastic anemia. To provide optimal pharmacological treatment of epilepsy, the type of seizure involved, the associated neurological abnormalities, and the physiological and behavioral side effects of antiepileptic drugs must be considered. The remainder of this paper will address the side effects of these compounds.

The physiological side effects of various anticonvulsants are generally well known, and are described elsewhere (Physicians’ Desk Reference, 1989; Rall & Schleifer, 1985; Woodbury, 1982). This information has been useful in selecting among antiepileptic drugs that are equally effective in seizure control, but differ with respect to their physiological side effects (Poling & Picker, 1987).

Interestingly, drugs from the same chemical class, that is, drugs that are structurally similar, may 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 (Rall & Schleifer,
1985). It is, nonetheless, a popular drug for treating all types of epilepsy except absence seizures. Another hydantoin, mephenytoin, may provide better control of tonic-clonic seizures than phenytoin. It may also cause less ataxia, gingival hyperlasia, gastric distress, and hirsutism than phenytoin (Rall & Schleifer, 1985). This has led some researchers to suggest the use of mephenytoin as an alternative to phenytoin (Gibbs et al., 1982). Serious side reactions (e.g., morbilliform rash, fever, lymphadonaphy, aplastic anemia, leukopenia, hepatotoxicity, periartheritis nodosa, and lupus erythmatosus) are, however, relatively common with mephenytoin (Kupferberg, 1982; Physicians’ Desk Reference, 1989; Rall & Schleifer, 1985) and there is a greater risk of toxicity associated with this agent. As a result, mephenytoin is the drug of choice only after other less toxic agents have been ineffective in controlling seizure activity (Kupferberg, 1982; Physicians’ Desk Reference, 1989; Rall & Schleifer, 1985).

Just as antiepileptic drugs within a given chemical class may differ with respect to their physiological side effects, they may also differ with respect to their behavioral actions. Although little attention has been paid to the behavioral side effects of these agents in the past, it has become increasingly evident that patients experience subtle behavioral side effects at doses that are at or below the suggested optimum therapeutic levels (SOTLs) (Gibbs et al., 1982). More critically, Gibbs et al. (1982) note that "in the worst cases, the failure to appreciate that elevated levels of hydantoins and barbiturates and possibly other antiepilepsy medications can result in a loss of seizure control has led to very serious long-term overmedication and irreversible central nervous system damage" (p. 314).

Recent investigations into the behavioral side effects of drugs have typically focused on two specific areas, the behavioral locus of drug action, and the behavioral mechanisms of action of the drug. The behavioral locus of drug action refers to the
observed changes in specific aspects of behavior following a drug's administration (Poling & Picker, 1987, p. 160). The behavioral mechanism of action is the general manner in which these changes are produced (Poling & Picker, 1987, p. 160). Most recent behavioral studies have examined the behavioral locus of drug action.

At present, the data on the behavioral locus of action of anticonvulsant drugs are inconclusive. Researchers (Gibbs et al., 1982; Poling & Picker, 1987; Stores, 1975) have noted that the existing research presents conflicting conclusions about the subtle behavioral side effects of these drugs. For example, conclusions about the behavioral side effects of phenytoin, a frequently studied anticonvulsant drug, differ widely (see Gibbs et al., 1982; and Poling & Picker, 1987). Research does suggest, however, that the more a study focused on attention, concentration, and short-term memory, the more likely it was to conclude that antiepileptic drugs cause subtle side effects (Gibbs et al., 1982).

Although many factors contribute to the inconsistencies which exist in the data on the behavioral side effects of anticonvulsant drugs, the problem of imposing adequate controls when studying clinical patients (Gibbs et al., 1982), and polypharmacy (Poling & Picker, 1987) have been identified as major barriers to the adequate investigation of the subtle behavioral side effects of these agents. In an effort to overcome these barriers, researchers have employed non-human animals as subjects, allowing investigators to examine the behavioral effects of individual drugs under experimentally controlled conditions. Several behavioral assays have been used to profile drug effects on many learned and unlearned behaviors (see Poling & Picker, 1987).

Phenytoin (Dilantin) is the most commonly prescribed antiepileptic drug for all seizure types except absence seizures (Poling & Picker, 1987; Rall & Schleifer, 1985). The behavioral effects of phenytoin on operant behavior in humans (Davis,
Poling, Wysocki & Breuning, 1981; Gay, 1984), as well as on the performance of non-humans under a number of behavioral assays, have been examined (for reviews see Kulig, 1980; and Poling & Picker, 1987).

Researchers have only recently begun to investigate the behavioral effects of mephenytoin in non-humans (Blakely, Starin & Poling, 1989; Delaney & Poling, 1987; Schlinger & Poling, 1988a, 1988b; Schlinger, Wilkenfield & Poling, 1988). No comparison of the behavioral effects of phenytoin and mephenytoin in humans has appeared. The recent investigations of the behavioral effects of mephenytoin on the performance of non-human animals do, however, permit some comparisons of the behavioral effects of these two drugs.

Under repeated acquisition procedures, both drugs appear to increase errors at moderate and high doses and produce dose-dependent decreases in the response rates of pigeons (Delaney & Poling, 1987; Picker & Poling, 1984; Poling, Blakely, White & Picker, 1986). That is, greater decrements in response rates were observed at larger doses.

Phenytoin and mephenytoin produce different behavioral effects under delayed-matching-to-sample procedures. Schlinger and Poling (1988b) reported that mephenytoin produced dose-dependent reductions in accuracy (percent correct responses). Further, they observed that acute administrations of low doses of mephenytoin increased response rates, while high doses decreased rates to below control means. Behavioral investigations of phenytoin showed that it either did not interfere with accuracy (Picker, White & Poling, 1985; Poling, Picker, Vande Polder & Clark, 1986), or only reduced accuracy at the highest doses administered (Karas, Picker & Poling, 1986). Moreover, high doses of phenytoin were reported to reduce response rates, but low doses had no effect on responding (Poling, Picker, Vande Polder & Clark, 1986; Picker, White & Poling, 1985).
Under fixed-consecutive-number schedules, both phenytoin and mephenytoin produce generally dose-dependent decreases in response rates and accuracy as measured by the percentage of reinforced runs (Picker, Leibold, Endsley & Poling, 1986b; Schlinger et al., 1988).

One recent study (Blakely et al., 1989) examined the effects of mephenytoin on the reaction time of pigeons. Reaction time was defined as the elapsed time from the change in color of a stimulus light to the release of a treadle. These investigators reported that mephenytoin produced generally dose-dependent increases in median reaction times and dose-dependent decreases in the percent of reinforced runs. The effects of phenytoin have not yet been examined under this assay.

Poling and Picker (1987) note that "the schedule of reinforcement under which behavior is maintained exercises powerful control over the rate and temporal pattern of responding" (p. 161). For many drugs, including anticonvulsants, the drug effects observed may be a function of the response rates maintained in the absence of drug, or may be rate-dependent (see McKearney & Barrett, 1978). Although many schedules of reinforcement may be useful in examining the rate-dependent effects of drugs, McKearney and Barrett (1978) note that fixed interval schedules may be especially useful because they engender and maintain a wide variety of response rates.

To date, one study has investigated the behavioral effects of mephenytoin on schedule-controlled behavior (Schlinger & Poling, 1988b). Schlinger and Poling (1988b) examined the effects of mephenytoin (40, 60, 80, and 120 mg/kg) on the performance of pigeons maintained under a multiple variable interval 60-sec extinction schedule of food delivery over a twelve hour session. Mephenytoin produced dose-dependent decreases in response rates for all subjects. Moreover, at the highest dose administered (120 mg/kg) responding decreased to zero or near zero.
levels during the third hour of the session and remained at that level for the duration of the session. These researchers reported the greatest decrement in response rates for all doses at a pre-session injection interval of 2 hours, but decrements were observed as long as 11 hours after administration.

Phenytoin has been reported to produce dose-dependent decreases in relatively high response rates in the performance of pigeons maintained by a fixed-ratio 50 schedule of reinforcement (Krafft & Poling, 1982a). It has also been found to decrease high response rates in the performance of rats maintained by a fixed ratio 30 schedule of reinforcement (Picker, Thomas, Koch & Poling, 1985), a multiple fixed ratio 20 fixed interval 60-sec schedule (Krafft, Lyon & Poling, 1982), and a variable interval schedule (Goldberg & Ciofalo, 1969). Moreover, it has been shown to reduce high rates of responding at doses that do not systematically affect low response rates in rats (Krafft et al., 1982; Picker, Thomas, Koch & Poling, 1985). These data are consistent with the clinical observations of Davis et al. (1981) who reported that with mentally retarded subjects, phenytoin decreased the rate of bicycle assembly maintained under a fixed ratio schedule of token delivery.

The purpose of the present study was to extend the work done on the behavioral effects of antiepilepsy drugs by examining the effects of acute and chronic administrations of mephenytoin on the performance of pigeons under a multiple fixed-ratio 50 fixed-interval 90-sec schedule of food delivery. This schedule permitted a comparison of the effects of mephenytoin on high rate responding characteristically produced by the FR 50 schedule and low rate responding characteristically produced early in the interval of the FI 90-sec schedule.
CHAPTER II

METHODS

Subjects

Three experimentally naive White Carneaux pigeons, maintained at approximately 80% of their free-feeding weight, served as subjects. Subjects were individually housed in a constantly illuminated room with unlimited access to grit and water.

Apparatus

Experimental sessions were conducted in three Lehigh Valley Electronics operant conditioning chambers. Each chamber measured 32 cm long, 36 cm high, and 35 cm wide. Three response keys, measuring 2.5 cm in diameter, were located 23 cm from the bottom of the front panel approximately 5.5 cm apart. Each key could be illuminated red or blue-green and required a force of approximately 0.2 N for operation. Only the center key was illuminated and operative during this study. An aperture measuring approximately 5 cm by 5 cm was centered horizontally on the front panel 7.5 cm above the floor. Subjects were allowed access to mixed grain through this aperture when the hopper was raised. When raised, the hopper was illuminated by a 7-W white bulb. A 7-W white bulb mounted on the center of the ceiling provided illumination during experimental sessions and a Grason-Stadler white noise generator provided masking noise.

The scheduling of experimental events and data collection were accomplished through the use of a Digital Equipment Corporation (Maynard, MA) PDP/8A
minicomputer located in a room adjacent to the chambers. Interfaecn and SUPERSKED software were obtained from State Systems Inc., Kalamazoo, Michigan.

Training Procedure

Subjects were initially trained to eat grain from the raised hopper. Once subjects did so consistently, they were exposed to a standard, forward-pairing, response-dependent autoshaping procedure. Under this procedure, 40 trials, separated by a variable 50-sec intertrial interval (ITI), were presented during each session. During each trial, the center key was illuminated either red or blue-green for 6 seconds. Key color on a given trial was randomly determined. A response to the lighted key produced the immediate offset of the key light and three seconds access to the raised hopper. If a subject did not respond to the lighted key, the key light was extinguished and the hopper was raised after the six second interval elapsed. Once responding was maintained on 90% of the trials under the autoshaping procedure, subjects were exposed to a multiple Fixed-Ratio Fixed-Interval (mult FR FI) schedule.

All training and subsequent experimental sessions were conducted seven days a week at approximately the same time each day. Each session was 30 minutes in duration and was comprised of three five-minute periods of the FI schedule alternating with three five-minute periods of the FR schedule. Each session began with 5 minutes of the FI schedule. The center key was illuminated blue-green during the FI components, and red during the FR components.

Initial training began with a mult FR 1 FI 1-sec schedule of food delivery. Subjects were allowed three seconds access to the raised hopper following the nth response under the FR schedule and following the first response after $t$ unit of time.
under the FI schedule. Once responding appeared stable at a given schedule value, the ratio and interval values were gradually increased both between and within sessions. All subjects were exposed to the terminal mult FR 50 FI 90-sec schedule after approximately 20 training sessions.

Behavioral Procedure

During the FI 90-sec schedule, the center key was illuminated for at least 90 seconds, and until the first response to the lighted key after the interval elapsed. Responses to the lit key during the 90-sec interval were recorded but had no programmed consequences. The first response after the 90 second interval extinguished the houselight and key lights and produced three seconds access to the raised hopper. The next trial, initiated by the onset of the house and key lights, began immediately following access to the raised hopper.

Once the subject had been exposed to the FI 90-sec schedule for five minutes, the key light was turned off and re-illuminated red, and the FR 50 schedule was initiated. Under this schedule, the fiftieth response to the lighted key extinguished the houselight and key lights and produced three seconds access to the raised hopper. The next trial began immediately after the hopper was lowered. Upon completion of the next five minute period, the key light color changed to blue-green and the FI 90-sec schedule was reinstated. The multiple schedule continued to alternate at five minute intervals for the duration of the 30 minute session. Within a given session, each subject was exposed to 15 minutes of the FR 50 schedule and 15 minutes of the FI 90-sec schedule of food delivery.
Pharmacological Procedure

**Acute Regimen**

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. Responding was considered stable when the response rates in each of three consecutive sessions differed no more than 10% from the mean response rates across those three sessions. When this criterion was met, acute dose-response determinations began.

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, eight hours prior to testing. Drug doses and the pre-session injection interval were selected on the basis of those used in previous investigations (Clark, Schlinger & Poling, 1987; Delaney & Poling, 1987; Schlinger et al., 1988). Each subject received two acute administrations of each dose of mephenytoin. Doses were presented in a random order that differed across birds. Prior to the first acute administration of mephenytoin, each subject received an injection of Dimethyl Sulfoxide (DMSO). All subsequent control injections consisted of 0.9% Sodium Chloride Isotonic Saline solution; prior data (Delaney & Poling, 1987) indicate that DMSO is not behaviorally active at the volume used in this study.

The acute regimen followed a BBCD sequence in which B represents baseline sessions, C represents sessions preceded by a control injection, and D represents sessions preceded by a single dose of mephenytoin. The stability criterion described
above was imposed prior to each acute administration, and one of the three sessions prior to each drug administration was a control session.

**Chronic Regimen**

Following the final acute administration, subjects were exposed to six baseline sessions of the mult FR 50 FI 90-sec schedule, followed by at least five consecutive sessions preceded by IM administrations of isotonic saline solution. Subjects received control injections until responding stabilized under both components of the schedule. Subjects were then exposed to a chronic regimen of daily injections of 120 mg/kg mephenytoin with three single challenge doses (240, 300, 360 mg/kg) of mephenytoin superimposed on the chronic schedule.

Subjects 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 FR 50 FI 90-sec schedule when given acutely. Following the tenth day of chronic exposure to 120 mg/kg, subjects were injected with a dose of 240 mg/kg. Thereafter, doses of 300 and 360 mg/kg were administered with ten days of chronic injections of 120 mg/kg between each challenge dose. Challenge doses were given in an ascending order because of possible toxic effects (e.g., death) at doses above 240 mg/kg. Following the final injection of 360 mg/kg, no other injections were given and subjects were exposed to the mult FR 50 FI 90-sec schedule until responding stabilized.
The primary dependent variables examined in this study were the number of responses per minute (response rates) under each component of the mult FR 50 FI 90-sec schedule of reinforcement, and the distribution (percentage) of responding within each 90 second fixed interval. In addition, postreinforcement pause times (i.e., average time elapsed from the completion of one FR 50 to the emission of the next response) and run rates (i.e., total responses/total time - postreinforcement pause time and latency to respond when conditions changed) were examined for the FR 50 component.

Figure 1 shows the effects of acute administrations of mephenytoin on response rates maintained by the FR 50 (upper panels) and FI 90-sec (lower panels) components of the multiple schedule for individual subjects and for subjects as a group. Control data points (Cl) represent the mean of ten control sessions; a single control injection was given prior to each of the ten acute dose administrations. Drug data points represent the mean of two administrations. Vertical lines represent the standard error of the mean (SEM).

In general, the effects of acute administrations of mephenytoin were consistent under the FR 50 and FI 90-sec schedules. Low doses (30 mg/kg, 60 mg/kg) produced minimal changes in performance under either component. Moderate doses (120 mg/kg, 160 mg/kg) produced differing effects across subjects and components. The highest dose administered, 240 mg/kg, reduced responding to zero or near zero levels under both components for all subjects.
Figure 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.
During acute control sessions, the FR 50 component maintained relatively high rates of responding for all subjects, with a group mean of 143 responses per minute and a standard error of 4.7. The most consistent effect observed during the acute phase was a significant reduction in FR response rates of all subjects at the highest dose administered (240 mg/kg). Low doses of mephenytoin (30 mg/kg, 60 mg/kg) had little behavioral effect on the FR response rate of any subject. Further, doses of 120 mg/kg and 160 mg/kg did not affect the third Subject's responding under the FR 50 schedule. Doses of 120 mg/kg mephenytoin produced a slight decrement in responding for Subject S1, and a significant reduction for Subject S2. Acute administrations of 160 mg/kg increased response rates to slightly above the control mean for Subject S1, but decreased response rates for Subject S2.

Under the FI 90-sec component, all subjects responded at moderate rates during control sessions, with a group mean rate of 43 responses per minute, and a standard error of 2.6. In general, acute administrations of mephenytoin produced inconsistent effects across subjects. Administrations of 30 mg/kg had little behavioral effect on the FI responding of two subjects (S2, S3), but increased the response rate of Subject S1. Doses of 60 mg/kg produced increases in FI responding for two subjects (S1, S2), but decreased responding for Subject S3 considerably. Doses of 120 mg/kg and 160 mg/kg mephenytoin produced significant increases in the response rates for two subjects (S1, S3), but decreased responding for Subject S2. Acute administrations of 240 mg/kg reduced response rates to zero or near zero levels for all subjects.

Repeated measures analysis of variance (Hopkins & Glass, 1978) of acute group data revealed a significant overall difference between mean group response rates during control and acute drug sessions. 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 post-chronic control sessions, during the tenth, twentieth, and thirtieth sessions of chronic exposure to 120 mg/kg mephenytoin, and during exposure to 240, 300 and 360 mg/kg challenge doses. Drug data points represent a single administration of a particular dose. Control data points at C2 represent the mean of all control sessions immediately prior to the chronic regimen. Control data points at C3 represent the mean of all baseline sessions (no injections) following the chronic phase. Vertical lines represent the standard error of the mean (SEM).

For all subjects, response rates during pre-chronic control sessions were similar to the rates maintained during acute control sessions under both components of the multiple schedule. The group mean response rates were 134 and 46 responses per minute under the FR 50 and FI 90-sec components respectively. Although considerable variability was evident across subjects during the chronic drug regimen, all subjects developed some degree of tolerance to the rate-reducing effects of mephenytoin under both components of the multiple schedule.

Initial chronic injections of 120 mg/kg, represented by data for day 10, produced reductions in FR responding for all subjects. Subsequent daily injections of 120 mg/kg, represented by data for days 20 and 30, produced decrements in FR responding for two subjects (S2, S3), but produced significant increases in response rates for Subject S1. By the thirtieth day of the chronic regimen, the first subject's response rates had increased from a pre-chronic control mean of 139 to a rate of 233 responses per minute. With the exception of Subject S2, these data are inconsistent with the effects of 120 mg/kg when administered acutely.
Figure 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 across 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 and 360 mg/kg) were given; data are presented for the tenth, twentieth, and thirtieth days of exposure to 120 mg/kg. Each challenge dose was given to each bird on a single occasion. Vertical lines represent standard errors.
Tolerance is most evident when the effects of the challenge dose of 240 mg/kg, administered after the tenth day of daily injections of 120 mg/kg, are compared with the effects produced by that dose when administered acutely. Acute administrations of 240 mg/kg significantly reduced FR responding for all subjects. Although the challenge dose reduced the responding of two subjects (S2, S3) to rates below those produced by daily injections of 120 mg/kg, response rates were well above those produced by 240 mg/kg when given acutely. The challenge dose of 240 mg/kg had little behavioral effect on the FR performance of Subject S1. Correlated t-tests (Hopkins & Glass, 1978) revealed that the group response rate under the FR 50 component, t(2) = 36.79, p<0.01, was significantly higher when 240 mg/kg was given as a challenge dose than when it was given acutely.

Tolerance was also evident at doses higher than those given acutely. Challenge doses of 300 mg/kg and 360 mg/kg, administered with ten days of chronic injections of 120 mg/kg between each dose, reduced FR response rates for two subjects (S2, S3), but rates were greater than those produced by acute administrations of 240 mg/kg. The same doses produced further increases in the response rates of Subject S1; the final challenge dose (360 mg/kg) increased Subject S1's response rate to 244 responses per minute, the highest rate observed during the study. During post-chronic baseline sessions, the mean FR response rate for all subjects returned to near pre-chronic control levels.

Although chronic drug administrations affected the performance of Subject S1 differently under the FR 50 and FI 90-sec components of the mult schedule, tolerance to the rate-reducing effects of mephenytoin was evident for all subjects under the FI component. Chronic administrations of 120 mg/kg did not significantly alter any subject's response rates under the FI 90-sec component. With the exception of
Subject S2, these data are consistent with the behavioral effects produced by that dose when administered acutely.

A challenge dose of 240 mg/kg mephenytoin reduced responding for all subjects to rates below that produced by ten daily administrations of 120 mg/kg, but well above the rates produced by 240 mg/kg when administered acutely. Correlated t-tests (Hopkins & Glass, 1978) revealed that the group response rate under the FI 90-sec component, t(2) = 15.33, p<0.01, was significantly higher when 240 mg/kg was given as a challenge dose than when it was given acutely.

Tolerance was also observed at the higher challenge doses. A challenge dose of 300 mg/kg reduced responding for all subjects, but for Subjects 1 and 3 the rates were higher than those produced by acute administrations of 240 mg/kg. The final challenge dose (360 mg/kg) produced response rates above the pre-chronic control means for all subjects. During post-chronic baseline sessions, the FI 90-sec schedule maintained response rates similar to those observed during pre-chronic control sessions.

Figure 3 shows the effects of selected doses of mephenytoin on the temporal distribution (percentage) of responding in each successive ten second bin of the 90 second fixed interval for individual subjects. Control data represent the mean of control sessions prior to each of the ten acute administrations. Drug data represent the mean of two administrations of 30 mg/kg and 160 mg/kg. A dose of 30 mg/kg was the lowest dose given acutely, and 160 mg/kg was the highest dose administered acutely that did not reduce responding to zero under either the FR 50 or FI 90-sec components.
Figure 3. Effects of Selected Doses of Mephenytoin on the Distribution of Responding Under the FI 90-sec Component of the Multiple Schedule.

Open circles represent the mean of all control sessions prior to acute administrations. Closed circles show the mean performance for two acute administrations of 30 mg/kg mephenytoin. Closed squares represent the mean performance for two doses of 160 mg/kg mephenytoin administered acutely.
Control data for all subjects indicate that, in the absence of drug, the percentage of total responses in each ten second bin increased gradually as the 90 second interval progressed. Acute administrations of 30 mg/kg did not systematically affect this characteristic pattern of responding. Administrations of 160 mg/kg mephenytoin altered the temporal distribution of responding for two subjects (S1, S2). This dose produced a "flattening" of the response distribution curve for Subject S1, such that the percent of total responses ranged from a mean of 8.5 to a mean of 13.5 percent during all nine of the 10 second bins of the 90 second interval. For Subject S2, 160 mg/kg produced a sharp peak in responding early in the interval (in the second and third bins), followed by a decline in responding as the interval progressed.

Table 1 shows the effects of acute administrations of mephenytoin on mean postreinforcement pause times and mean run rates under the FR 50 component for individual subjects. Postreinforcement pause time is defined as the average time elapsed from the completion of one FR 50 to the emission of the next response. Run rate is defined as the total number of responses divided by the total time - postreinforcement pause time and latency to respond when conditions changed. Control data represent the mean (and one standard error) of all acute control sessions. Drug data represent the mean of two administrations of the dose indicated. Acute administrations of mephenytoin did not significantly affect postreinforcement pause times or run rates of two subjects (S1, S3). Data for Subject S2 show generally dose-dependent increases in postreinforcement pause times, and inconsistent effects with respect to run rates.
Table 1

Effects of Mephenytoin on Mean Postreinforcement Pause Times and Run Rates
Under the Fixed-Ratio Component of the Multiple Schedule

<table>
<thead>
<tr>
<th>Mephenytoin (mg/kg)</th>
<th>C1</th>
<th>30</th>
<th>60</th>
<th>120</th>
<th>160</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>1.3 (0.1)</td>
<td>1.6</td>
<td>1.2</td>
<td>2.2</td>
<td>1.5</td>
<td>0.0</td>
</tr>
<tr>
<td>S2</td>
<td>3.5 (0.4)</td>
<td>3.9</td>
<td>5.0</td>
<td>34.6</td>
<td>16.0</td>
<td>20.1</td>
</tr>
<tr>
<td>S3</td>
<td>4.0 (1.1)</td>
<td>3.9</td>
<td>5.2</td>
<td>3.6</td>
<td>4.8</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Mean Postreinforcement Pause Time (sec)

Mean Run Rates (Responses/Min)

<table>
<thead>
<tr>
<th></th>
<th>S1</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>168 (3.8)</td>
<td>179</td>
<td>176</td>
<td>147</td>
<td>194</td>
</tr>
<tr>
<td></td>
<td>186 (6.8)</td>
<td>194</td>
<td>209</td>
<td>134</td>
<td>235</td>
</tr>
<tr>
<td></td>
<td>133 (4.1)</td>
<td>134</td>
<td>130</td>
<td>131</td>
<td>135</td>
</tr>
</tbody>
</table>

Control values represent the mean (and one standard error) of all acute control sessions. Drug data represent the mean of two administrations of the dose indicated.
CHAPTER IV

DISCUSSION

Investigations reviewed elsewhere (Kulig, 1980; Poling & Picker, 1987) indicate that there often are qualitative and quantitative differences in the behavioral effects of drugs from different chemical classes. Recent evidence suggests that there frequently are differences in the behavioral effects of anticonvulsant drugs in the same class, that is, when they are structurally similar (Delaney, Pellettiere, Schlinger & Poling, 1988; Delaney & Poling, 1987; Picker et al., 1986; Picker & Poling, 1984; Poling et al., 1986; Schlinger et al., 1988). Whether drugs from the same chemical class produce dissimilar behavioral effects may depend upon the assay employed. For example, the succimides, ethosuximide and methsuximide, have dissimilar effects under a repeated acquisition procedure and a fixed-consecutive-number procedure (Delaney & Poling, 1987; Picker et al., 1986b; Picker & Poling, 1984; Poling, Blakely, White & Picker, 1986; Schlinger et al., 1988), but they produce comparable effects under a mult FR 50 FI 90-sec schedule (Delaney et al., 1988; Gibbs et al., 1982).

Phenytoin and mephenytoin, both hydantoins, have previously been shown to produce similar effects under a repeated acquisition procedure (Delaney & Poling, 1987; Picker & Poling, 1984; Poling, Blakely, White & Picker, 1986) and under a fixed-consecutive-number schedule (Picker et al., 1986a; Schlinger et al., 1987), but produce dissimilar effects under delayed-matching-to-sample procedures (Karas et al., 1986; Picker, White & Poling, 1985; Poling, Picker, Vande Polder & Clark, 1986; Schlinger & Poling, 1988b).
The present findings indicate that mephenytoin, at a sufficiently high dose, reduces responding under both components of a mult FR 50 FI 90-sec schedule of food delivery, and that tolerance develops to this effect. Schlinger and Poling (1988b) reported similarly that mephenytoin produced dose-dependent decreases in the response rates of pigeons under a mult VI 60-sec EXT schedule.

The effects of phenytoin under a mult FR 50 FI 90-sec schedule have not been examined in pigeons. High doses of phenytoin have, however, been shown to decrease responding under both components of a mult FR 20 FI 60-sec schedule (Krafft et al., 1982), and to reduce response rates under simple FR 50 schedules (Krafft & Poling, 1982a) simple fixed ratio 30 schedules (Picker, Thomas, Koch & Poling, 1985) and a simple variable interval schedule (Goldberg & Ciofalo, 1969).

The effects of many drugs have been reported to be rate-dependent (McKearney & Barrett, 1978; Sanger & Blackman, 1976; Thompson, Dews & McKim, 1981). That is, the direction and magnitude of the observed drug effects are determined by the (local) rate of responding in the absence of drugs, which may be determined by the schedule under which responding is maintained (Poling & Picker, 1987). If the effects of mephenytoin are rate-dependent, one would predict that mephenytoin would decrease the higher response rates engendered by the FR 50 component at doses which did not affect, or increased responding under the FI 90-sec component. The overall data on the effects of acute administrations on response rates do not appear to demonstrate this phenomenon. Low doses of mephenytoin (30, 60 mg/kg) did not significantly alter responding under either component of the multiple schedule. A dose of 120 mg/kg reduced response rates under both components, and a dose of 240 mg/kg reduced responding to zero or near zero levels for all subjects under both the FR 50 and FI 90-sec components.
Detailed analyses of the effects of acute administrations of mephenytoin on the distribution of responding under the FI 90-sec component of the multiple schedule do, however, provide some evidence that the effects of mephenytoin may be rate-dependent. A dose of 30 mg/kg did not alter the distribution of responding for any of the subjects. The highest dose which did not reduce responding to zero or near zero levels (160 mg/kg) did alter the distribution of responding for two subjects. This dose increased low response rates early in the 90-sec interval and decreased high response rates later in the interval.

Comparison data on the effects of phenytoin on schedule-controlled behavior are, at present, unavailable. Phenytoin has, however, been found to decrease high rate responding maintained under a FR 30 and FR 20 schedule at doses that had no reliable effect on low response rates maintained by an IRT>15-sec schedule in rats (Krafft et al., 1982; Picker, Thomas, Koch & Poling, 1985). When compared to those of the present study, these results suggest that phenytoin and mephenytoin may produce similar rate-dependent effects on schedule-controlled performance.

One primary reason for investigating the behavioral effects of antiepilepsy medications in nonhumans is to better understand the possible side effects of such drugs in humans (Poling & Picker, 1987). Since most humans who take antiepilepsy drugs ingest these medications on a chronic basis (Rall & Schleifer, 1980; Woodbury, 1982), those nonhuman studies which investigate the chronic as well as acute effects of anticonvulsant drugs may provide more valuable information than investigations of acute effects alone. One phenomenon which is of particular interest when a drug is ingested chronically is whether tolerance develops to the main or side effects of that drug. Tolerance refers in general to diminished responsiveness to a drug with repeated exposure, and can be demonstrated by showing that the effects of a given dose lessen across administrations (Krafft & Poling, 1982b).
The present findings suggest that tolerance did develop to the rate-decreasing effects of mephenytoin under a mult FR 50 FI 90-sec schedule of food delivery. When administered acutely, a dose of 240 mg/kg reduced responding to zero or near zero levels for all subjects under both conditions of the mult schedule. Challenge doses of 240, 300 and 360 mg/kg, administered following chronic exposure to 120 mg/kg, produced response rates significantly higher than those produced by acute administrations of 240 mg/kg under both components of the schedule. No other data on the effects of chronic administrations of mephenytoin on response rates under mult FR 50 FI 90-sec schedules have been reported.

Krafft and Poling (1982a) reported that tolerance developed to the rate reducing effects of phenytoin (10 and 20 mg/kg) under an FR 50 schedule following chronic exposure to that drug. Tolerance to the rate-decreasing effects of phenytoin has also been reported under delayed-matching-to-sample procedures (Poling, Picker, Vande Polder & Clark, 1986; Schlinger & Poling, 1988a), and repeated acquisition procedures (Poling, Blakely, White & Picker, 1986). It appears that tolerance or partial tolerance develops to the rate-reducing effects of both mephenytoin and phenytoin.

A pre-session injection interval of 8 hours was selected for the current study based on previous behavioral investigations of mephenytoin (Clark et al., 1987; Delaney & Poling, 1987). Schlinger and Poling (1988b) reported the greatest reduction in responding for all doses of mephenytoin after a 2 hour pre-session injection interval. These data suggest that lower doses of mephenytoin (30 and 60 mg/kg) may have reduced responding under the mult FR 50 FI 90-sec schedule, but these reductions were not observed due to the length of the pre-session injection interval employed in the current study.
The present study reports data based on three pigeons as subjects. As such, any general conclusions based on these particular data are unwarranted. These data, however, when considered with the existing literature on the behavioral effects of phenytoin and mephenytoin, suggest that these drugs produce similar effects on the behavior of nonhuman subjects under several behavioral assays including multiple schedules of food delivery.

The extent to which the present results apply to the clinical use of mephenytoin with humans is unclear. The doses examined in this study were higher than those used to manage seizures in humans (Gadow & Poling, 1988, pp. 183-185), but the metabolism of pigeons differs considerably from that of humans. There is, however, considerable support for the notion that the behavioral drug effects observed in nonhumans may also be observed in humans (Poling & Picker, 1987). Poling and Picker (1987) conclude:

We assume that drug effects are similar across species, an assumption that is empirically well supported: Insofar as can be determined, behavioral drug effects in humans and nonhumans are much the same under comparable conditions. There is nothing about human behavior that makes it uniquely sensitive or impervious to drugs, therefore studies of nonhumans can yield information useful in accounting for drug effects in our own species (p.187).

Although the results presented in this study contribute to the existing literature on the behavioral effects of mephenytoin, there is still much to be learned. The capacity of the doses of mephenytoin examined in the present study to block seizures in pigeons is unknown. An examination of the effects of these doses on induced seizures would, therefore, be valuable. Schlinger and Poling (1988b) suggest that the rate-reducing effects of mephenytoin may be greatest at a pre-session injection interval of 2 hours. At a pre-session injection interval of 8 hours, only the highest dose administered reduced response rates considerably. A re-examination of the time course of action of mephenytoin may reveal that a different pre-session injection
interval is optimal for examining the subtle behavioral effects of low doses of this drug. Finally, the data on whether the effects of mephenytoin are rate-dependent are inconclusive. Further research on the effects of mephenytoin on schedule-controlled behavior may be valuable.
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