The Effects of Methsuximide and Mephenytoin on the Repeated Acquisition Performance of Pigeons

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THE EFFECTS OF METHSUXIMIDE AND MEPHENYTOIN ON THE REPEATED ACQUISITION PERFORMANCE OF PIGEONS

by

Dawn D. Delaney

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THE EFFECTS OF METHSUXIMIDE AND MEPHENYTOIN ON THE
REPEATED ACQUISITION PERFORMANCE OF PIGEONS

Dawn D. Delaney, M.A.
Western Michigan University, 1987

Learning impairment is a potentially serious side effect of antiepilepsy medications. The present study investigated the effects of methsuximide and mephenytoin on learning in pigeons performing under a repeated acquisition procedure. Given acutely, methsuximide (25, 50, 75, 100 mg/kg) and mephenytoin (60, 120, 240 mg/kg) produced generally dose-dependent decreases in rates of responding; increases in percent errors were largest at doses that produced the greatest decrease in response rate. An analysis of the within-session distribution of errors revealed that certain doses of each drug impaired learning. With chronic exposure, appreciable tolerance developed to the behavioral effects of mephenytoin, but not to those of methsuximide. The physiological mechanism responsible for this outcome is unknown.
ACKNOWLEDGEMENTS

My thanks go out to Alan Poling for his advice, friendship, and unfailing confidence in my abilities. The unselfish manner in which he shared his knowledge (and computer!) have not gone unappreciated. As I continue along my academic journey, a part of him goes with me.

Thanks, too, to Wayne Fuqua and Jack Michael for their guidance and friendship which extend far beyond the completion of this thesis. Appreciation is also expressed to the members of the Behavioral Pharmacology Laboratory for sharing in the successes and failures which are an inevitable part of learning.

Special thanks are due my parents, Bob and Linda Delaney, who have loved, encouraged, and believed in me. This thesis is dedicated to them.

Dawn D. Delaney
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INTRODUCTION

A frequently cited definition of epilepsy is provided by Rail and Schleifer (1980):

Epilepsy is a collective designation for a group of chronic central nervous system (CNS) 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. 448)

The EEG (electroencephalograph) measures the amplitude and pattern of electrical (i.e., neuronal) activity at various parts of the brain; by comparing a patient's EEG recordings to control recordings, the neurological locus of seizure activity can be determined. Analysis of EEG patterns, combined with data on the clinical manifestations of the attacks, serves as the basic method of modern differential diagnosis of the epilepsies (E. L. Gibbs, T. J. Gibbs, F. A. Gibbs, E. A. Gibbs, S. Dikman, & B. P. Herrmann, 1982).

Hauser (1978) estimates that the prevalence of all forms of epilepsy combined is 0.3% to 0.6% in the general population, although the Epilepsy Foundation of America (1975) cites a considerably higher prevalence rate of 2%. Among the mentally retarded, the prevalence is greater—most estimates place the prevalence of epilepsy at 20-35% in this population (Aman & Singh, 1983)—with frequency estimates rising rapidly as the degree of mental retardation increases. Those cases where no known cause for the seizures can be found are termed primary (or idiopathic) epilepsy; secondary (or symptomatic) epilepsy
designates cases where such factors as trauma, neoplasm, infection, developmental abnormalities, cerebrovascular disease, or various metabolic conditions contribute to the etiology (Rall & Schleifer, 1980). The majority of cases of epilepsy are of the primary type.

Although other treatments, such as behavior modification (see Krafft & Poling, 1982), dietary management, and neurosurgery are occasionally used successfully, pharmacotherapy has been the principle, as well as most effective, treatment for epilepsy (Rall & Schleifer, 1980; Jones & Woodbury, 1982). With drug treatment it is generally held that complete control of seizures can be achieved in up to 50% of patients and possibly another 25% can be improved significantly (Meinardi et al., 1977). The degree of success is largely dependent on the type of seizure and the extent of associated abnormalities. (Rall & Schleifer, 1980, p. 451)

Classification of Seizures

The drugs prescribed to treat epilepsy are selective for seizure type, thus the application of appropriate drug therapy requires accurate classification of seizures (Gibbs et al., 1982). Seizures are generally grouped into two categories: partial and generalized. Partial (or focal) seizures are distinguished from generalized seizures by local onset. That is, the abnormal electrical activity associated with partial seizures begins in a circumscribed part of the cerebral hemisphere, whereas generalized seizure activity occurs on both sides of the brain and its origin is not localized in either cerebral hemisphere. Partial and generalized seizures can be distinguished on the basis of EEG records.
Partial seizures are divided into three subgroups: simple, complex, and secondarily generalized. Simple partial seizures (also referred to as cortical focal seizures) are characterized by retention of normal consciousness, high localization of attack (e.g., jerking in one arm), and limitation to one hemisphere. The particular cortical area producing the abnormal discharge determines other signs and symptoms. Complex partial seizures (temporal lobe and psychomotor seizures) entail impaired consciousness and a wide range of motor responses. Such seizures are most common in older children and adults, have a duration of several minutes, and may be preceded by an aura, which frequently takes the form of a peculiar sensation (e.g., smell or taste) or sense of impending doom. These auras serve to warn the individual of possible progression to altered consciousness. Any type of partial seizure may progress to a generalized tonic-clonic seizure, that is, become secondarily generalized (Porter, 1982).

Generalized seizures are more heterogeneous than partial seizures. The most common generalized seizure is the tonic-clonic (also termed grand mal, or major motor), which occurs in two phases. The tonic phase, which appears first, is manifested as generalized muscle rigidity, during which consciousness is lost, breathing grows heavy and irregular, and urinary incontinence is sometimes exhibited.

The second, clonic phase is characterized by acute muscle spasms (most readily observed in the muscles of the jaw and legs), which gradually wane and cease, leaving the individual disoriented and fatigued. Tonic-clonic seizures, too, are occasionally preceded by
auras. Because it results in major convulsions and is followed by a prolonged depression of all central functions, the generalized tonic-clonic seizure presumably involves more neuronal systems than any other type of seizure.

Several other types of generalized seizures can also be distinguished. These include absence seizures, atonic seizures, clonic seizures, and infantile spasms. Absence (petit mal) seizures typically begin in childhood or adolescence, and are characterized by a brief (usually less than 10-15 sec) interruption of consciousness, often (but not necessarily) accompanied by mild clonic jerking varying from eyelid blinking to jerking of the entire body. Such seizures are noted for their brief and abrupt nature. In the majority of cases where absence is the only seizure pattern, seizures cease to be a clinical problem by 20 years of age (Sherwin, 1982). Atonic seizures are associated with sudden loss of postural tone and some individuals wear helmets for protection against resultant falls. Clonic seizures and the myoclonias are particularly heterogeneous, and are marked by rhythmic contractions of all muscles, loss of consciousness, and various autonomic manifestations. Symptoms of clonic jerking often accompany other seizure types. Infantile spasms are usually manifested by sudden and often repetitive jerks of the extremities and torso. In 90% of affected individuals, seizure activity begins before the age of one year, and is accompanied by progressive mental deterioration.
Drug Treatment of Seizures

At present, 17 different antiepilepsy drugs are marketed in the United States (Swinyard, 1982), although the majority of them are prescribed infrequently. These agents are grouped by chemical structure (e.g., as barbiturates, hydantoins, succinimides, oxazolidinediones, and benzodiazepines), and drugs with similar chemical structures typically have similar clinical applications (Woodbury, Penry, & Pippenger, 1982). The most commonly prescribed antiepilepsy drugs are phenytoin (Dilantin), primidone (Mysoline), and phenobarbital (Luminal). The precise biochemical mechanisms through which specific antiepilepsy medications produce their effects are poorly understood. However, there are two general ways in which such drugs may reduce seizure activity. As discussed by Rail & Schleifer (1980), one is by preventing or attenuating the excessive electrical activity of neurons at focal sites where seizures are initiated. The other is by preventing the spread of excitation from focal sites to surrounding neurons. Most, if not all, antiepileptic agents presently available act at least in part by the second mechanism, since all modify the ability of the brain to respond to various seizure-evoking stimuli (Rail & Schleifer, 1982).

Unfortunately, the drugs used to treat epilepsy "not only fail to control seizure activity in some patients, they frequently cause side effects that range in severity from minimal impairment of the central nervous system to death from aplastic anemia" (Rail & Schleifer, 1980, p. 451). The physiological side effects of various
Anticonvulsant medications are generally well known (e.g., Rall & Schleifer, 1980; The Physicians' Desk Reference, 1984; Woodbury et al., 1982), but less attention has been paid to the possible behavioral side effects of such drugs. At present, there is an emerging body of evidence indicating that most, if not all, antiepilepsy drugs can adversely affect learning, memory, and other higher intellectual functions (Gibbs et al., 1982; Woodbury et al., 1982).

It is quite possible that all of the available anticonvulsant medications produce adverse behavioral side effects, since all are simple chemical compounds capable of altering neuronal activity to the extent of preventing clinical seizures (Gibbs et al., 1982). The results of clinical investigations concerned with the behavioral effects of anticonvulsants are generally inconclusive, however, due in part to the methodological difficulties inherent in studying clinical patients (Gibbs et al., 1982). Among the factors that complicate clinical drug studies in humans are: (a) inability to withhold medication due to the risk of increasing seizure frequency and the negative behavioral side effects of seizures themselves; (b) variability in individual susceptibility to drugs and their levels; and (c) problems in using normal controls for drug testing (Gibbs et al., 1982). Furthermore, many epileptic patients receive more than one type of medication; thus, polypharmacy makes it difficult to assess the behavioral side effects of the individual agents (Gadow, 1986).

These factors have limited investigations of the behavioral effects of anticonvulsants in humans. In general, methodological shortcomings render the findings of the available studies difficult.
to interpret (Gibbs et al., 1982), and methodological differences across investigations (e.g., in doses examined, types of subjects employed, and dependent measures) result in disparate findings. Gibbs et al. (1982) have observed, however, that "the more weight a study placed upon attention, concentration, and short-term memory, the more likely it was to conclude that an antiepilepsy medication caused subtle side effects" (p. 305). Thus, despite the apparent weaknesses in the majority of clinical drug evaluations on the behavioral effects of antiepilepsy drugs, one cannot ignore the implication that these agents can, in fact, have a direct effect on the intellectual capabilities of epileptic patients.

In view of the difficulties inherent in conducting clinical investigations with human subjects, it is not surprising that investigations of the behavioral effects of anticonvulsant drugs in non-human subjects have recently appeared (e.g., Krafft, Cleary, & Poling, 1983; Paule & Killam, 1979; Picker & Poling, 1984; Picker, White, & Poling, 1985; Poling & Appel, 1979; Poling, Picker, Vande Polder & Clark, 1986; Weinberger & Killam, 1978). These studies have revealed that there are qualitative as well as quantitative differences in the effects of antiepilepsy medications. Moreover, whether a particular anticonvulsant drug disrupts behavior at a given dose depends upon how the behavior in question is maintained.

Rationale for the Present Study

In the present study, the effects of methsuximide and mephenytoin, two antiepilepsy drugs whose preclinical behavioral pharmacology is
unknown, were investigated using a repeated acquisition procedure. Methsuximide (Celontin), a succinimide derivative, was introduced in the mid-1950s, and was found to have a broad spectrum of anticonvulsant activity. According to Porter and Kupferberg (1982), early investigators thought that methsuximide was useful in treating "psychomotor seizures" (Cordoba & Strobos, 1956), both "petit mal" and "psychomotor seizures" (French, Rey-Bellet, & Lennox, 1958), "petit mal" seizures (Zimmerman, 1956), partial seizures (Dow, Macfarlane, & Stevens, 1958), and a variety of partial and generalized seizures (Scholl, Abbott, & Schwab, 1959). At present, methsuximide, along with its near relatives ethosuximide and phensuximide, is used primarily to manage absence seizures.

The physiological side effects of methsuximide have not been carefully studied. It has been reported, however, that methsuximide can produce nausea, anorexia, headaches, hiccoughs, drowsiness, and dizziness in some individuals (Rail & Schleifer, 1980). Methsuximide (as well as the other succinimides) may produce blood disorders such as pancytopenia (a reduction in all cellular elements in the blood) and agranulocytosis (extreme reduction of white blood cells). Such blood dyscrasias are a significant, but rare, side effect of the succinimides.

The other antiepilepsy medication investigated in the present study is mephenytoin. Mephenytoin (Mesantoin) has been used successfully for more than thirty years to control seizures (Kupferberg, 1982). It is most effective in the treatment of generalized tonic-clonic seizures, and has also been shown to satisfactorily control
all types of seizures except absence (Gadow, 1986). However, serious dose-related toxicity has hampered its widespread use. Among mephenytoin's most serious physiological side effects are pancytopenia and irreversible aplastic anemia (reduced red blood cells due to disorders of the bone marrow); the latter is fatal in some patients. Other adverse actions include skin rash, fever, generalized adenopathy (swelling and morbid change in lymph nodes), leukopenia (abnormal decrease of white blood corpuscles), and ataxia. The behavioral actions of mephenytoin have yet to be adequately examined.

Due to a lack of well-controlled research, the behavioral effects of methsuximide and mephenytoin are unclear. A potential behavioral action of anticonvulsant drugs that is especially troublesome is disruption of learning (Gibbs et al., 1982). The repeated acquisition of response chains (or simply, repeated acquisition) procedure is favored by behavioral pharmacologists for examining drug effects on learning and was used for that purpose in the present study.

There exists no universally agreed upon definition of learning. However, from a behavioral perspective, learning refers to changes in an organism's behavior as a result of operant or respondent conditioning (Poling, 1986). Similarly, "the proper domain of learning includes any transition that results from changes in the environmental contingencies maintaining behavior" (Sidman, 1960, pp. 118-119). Although there are many ways to study learning and drug effects thereon, few procedures, other than repeated acquisition, allow for a within-subject analysis.

Boren first described the repeated acquisition procedure in
1963; he also conducted the first study of drug (methylphenidate and magnesium pemoline) effects on learning as assayed by this procedure (Boren, 1967). Prior to this time, the experimental design commonly employed for studying learning (or acquisition) required an independent group of subjects for each value of the independent variable. Boren's repeated acquisition procedure allowed for repeated assessment of learning in individual subjects, and produced a steady state of re-learning which was then used as a baseline to study various independent variables, including drugs.

In Boren's (1967) pioneering study of drug effects on learning, rhesus monkeys were trained with food reinforcement in a chamber containing 12 levers arranged in four groups of three. Food delivery was dependent upon emitting a sequence of four spatially-defined responses. The session began with illumination of the lights over one group of three levers. A correct response extinguished the lights and advanced the chain to the second link, in which the lights over the second group of three levers were illuminated and another response was designated as correct. A correct response in the second link advanced the sequence to the third link; a correct response in the third link advanced the sequence to the fourth and final link. In the fourth link, a correct response was followed by food delivery, after which the sequence began anew (i.e., the same sequence was in effect for the entire session). In all components, an incorrect response (i.e., pressing a lever that was not part of the reinforced chain) was followed by a brief timeout, after which the same lights were illuminated as before the timeout.
In an effort to establish a baseline of repeated acquisition, Boren changed the four-response sequence from session to session. After prolonged daily exposure to these conditions, each subject reached a steady state in terms of the number of errors made in learning the different chains, as well as the pattern of acquisition. This steady state then served as a baseline for assessing the effects of methylphenidate and magnesium pemoline.

Since this time, numerous modifications to Boren's original procedure have appeared. Thompson (1973), for example, slightly altered Boren's procedure for use with pigeons. In this modification, the repeated acquisition procedure was kept functionally similar to Boren's original; however, keypecks were the operant response, only three response options were available, and links of the chain were differentiated by color rather than by location. In each session, the pigeon's task was to learn a new four-response sequence in which correct responses involved pecking one of three keys. The key designated as correct depended upon the color of key illumination, which changed as the sequence advanced. As occurred under the original procedure, steady-state performance in terms of total errors per session and pattern of acquisition was eventually reached under these conditions.

Poling and associates (Picker & Poling, 1984; Poling, Blakely, White, & Picker, 1986) have previously used a repeated acquisition procedure much like that described by Thompson (1973) to examine the effects of phenytoin, ethosuximide, valproic acid, phenobarbital, and clonazepam on learning in pigeons. With the exception of ethosuximide, each of these anticonvulsants substantially interfered with learning.
The purpose of the present study was to extend this line of research by examining the effects of two other antiepilepsy medications, mephenytoin and methsuximide. A basic tenet of pharmacology is that, where two or more medications are therapeutically equivalent, the one with the fewest (or mildest) side effects is preferred. By implication, studies of the behavioral effects of antiepilepsy drugs in nonhumans may provide information concerning untoward side effects in epileptic humans.
METHODS

Subjects

Seven adult female White Carneaux pigeons served as subjects. Four (MS1, MS4, MP2, MP3) were experimentally naive, and three (MS2, MS3, MP1) were used in a previous study investigating the effects of other anticonvulsants under a repeated acquisition procedure (Picker & Poling, 1984). All birds were obtained from the Palmetto Pigeon Plant (Sumter, SC) and were maintained within 10 g of 80% of their free-feeding weights (80% values were 440 g for MS1, 425 g for MS2, 490 g for MS3, 420 g for MS4, 440 g for MP1, 540 g for MP2, and 440 g for MP3). Each bird was individually housed with unlimited access to grit and water in a constantly illuminated room.

Apparatus

Six operant conditioning chambers, measuring 32 cm long, 36 cm high, and 35 cm wide, were employed. In each chamber, three response keys measuring 2.5 cm in diameter were located 23 cm from the bottom of the intelligence panel, approximately 5.5 cm apart. Each key could be illuminated in yellow, white, red, and blue-green. A minimum pressure of 0.2 g was required for key operation. An aperture centered horizontally on the intelligence panel 7.5 cm above the floor allowed access to a hopper filled with mixed grain when the hopper was raised. The hopper, when raised, was illuminated by a 7-w white bulb. A 7-w bulb (houselight) mounted 33 cm from the chamber
floor provided ambient illumination and a white noise generator provided masking noise.

Programming of experimental events and data collection were accomplished through the use of a Digital Equipment Corporation (Maynard, MA) PDP8/A minicomputer using interfacing and software (SUPERSKED) provided by State Systems, Inc. (Kalamazoo, Ml).

Behavioral Procedure

Before the start of the experiment proper, the four experimentally naive subjects (i.e., MS1, MS4, MP2, MP3) were exposed to a forward pairing autoshaping procedure (Brown & Jenkins, 1968). Each autoshaping trial consisted of a 6-sec illumination of one of the three keys in yellow, blue-green, white, or red followed by 4-sec access to the raised food hopper. Presentation of each stimulus (key color) occurred under a random-time 45-sec schedule. Both the order in which the stimuli were presented and the keys where they appeared were randomized. Each session terminated after 40 autoshaping trials or 45 minutes, whichever came first. At the completion of eight autoshaping sessions, all subjects consistently pecked the keys when illuminated in any of the four colors.

Following preliminary keypeck training, food delivery (3-sec access to the raised hopper) was made dependent on the completion of a 4-response chain. Each link (component) in the chain (response sequence) was correlated with a different exteroceptive stimulus (key color) and the correct response for each component was defined by spatial locus. Throughout the study, yellow was associated with the
first component, blue-green with the second, white with the third, and red with the fourth and final component.

Initially, within each component only the key designated as correct was illuminated with the color correlated with that component in the chain; the other two keys remained dark. A keypeck on the illuminated key darkened the keylight and produced a 0.5-sec flash of the hopper light (intended to serve as a conditioned reinforcer, although the extent to which it did so was not determined), followed immediately by the illumination of one of the previously darkened keys in the color correlated with the next component in the chain. Keypecks to the darkened keys had no programmed consequences. The keys on which the stimuli appeared (and thus the response designated as correct) were selected according to three criteria specified by Boren (1963; Boren & Devine, 1968), and outlined by Thompson (1973). First, a correct color position in one session was not repeated in the following session. Second, the correct position in one component was not repeated in the next (e.g., a response sequence of Left (L), Left (L), Right (R), Center (C) was never programmed), although each position (i.e., L, R, C) occurred at least once in the 4-response sequence. Third, within a set of six sequences, each key was lighted equally often (twice) in each color. The set utilized in the present study included the following sequences: LRCR, CLRL, LRLC, RCRL, CLCR, RCLC. The same response sequence was repeated throughout a given session, and at the completion of the 4-response chain, the red keylight was darkened and mixed grain was made available for 3 sec.

After each bird consistently completed the response chain (i.e.,
received >20 reinforcers in a 60-min session) in the manner described above, the next day's session was programmed to illuminate all three keys simultaneously in red during the fourth component. Here, the response designated as correct continued to be followed by food delivery (i.e., 3-sec access to grain); however, incorrect responses (i.e., pecking either of the other two keys) were followed by a 3-sec timeout, during which the keylights and houselight were darkened and responses had no programmed consequences. Incorrect responses (errors) did not reset the response chain; that is, the stimuli presented after the timeout (and the response designated as correct) were identical to those arranged at the time of the error.

These conditions remained in effect for each bird until 20 or more reinforcers were delivered for two consecutive 60-min sessions. If the number of reinforcers was < 20 for either of two consecutive sessions, the following session was again programmed to illuminate only the key designated as correct in the fourth component. Following two consecutive sessions with all keys illuminated simultaneously in red during the fourth component, the chain was extended so that all three keys were also illuminated simultaneously in white during the third component. During the following daily sessions, the chain continued to be extended until all three keys were also illuminated in blue-green during the second component and then in yellow during the first component. Again, two consecutive sessions with >20 reinforcers were required prior to each extension of the chain.

After a bird received 60 food deliveries per session during three consecutive 60-min sessions, the number of 4-response sequences
required to produce food delivery was gradually increased from 1 to 5. At the latter value, completion of each 4-response sequence was followed by a 0.5-second flash of the hopper light, but food delivery only followed completion of the fifth 4-response sequence (i.e., the schedule could be conceptualized as a second-order FR5 [FR4] with brief stimuli added). Birds with a history of responding under the repeated acquisition procedure were only exposed to this condition, which was in effect during the balance of the study for all subjects. Sessions terminated after 1-hour or 60 food deliveries, whichever came first, and were conducted 6 days per week, at approximately the same time each day.

Dependent measures recorded during each experimental session were response rate, total number of responses, the percentage of total responses that were incorrect (errors), and the number of errors made before the delivery of each reinforcer. This latter measure provided for a within-session analysis of error reduction, as well as a means for comparing drug data with appropriate control data. Omitting this measure would introduce a potential confound, for if a drug were to slow responding of a bird so that few reinforcers were obtained, it might appear that learning was impaired relative to control sessions in which far more reinforcers were obtained (Picker & Poling, 1984).

Pharmacological Procedure

After the percentage of errors per session for individual birds showed no obvious trend across sessions (60–85 sessions for the four
experimentally naive birds, 10-40 sessions for the three with an experimental history), the acute effects of methsuximide and of mephenytoin were evaluated. Four doses of methsuximide (25, 50, 75, and 100 mg/kg) and vehicle controls were injected intramuscularly 30 minutes before each experimental session, at an injection volume of 1 ml/kg. Three doses of mephenytoin (60, 120, and 240 mg/kg) and vehicle controls were injected intramuscularly 9 hours prior to each experimental session at a 1 ml/kg injection volume. Drug doses and the presession injection times were selected on the basis of time course determinations conducted prior to the experiment proper. For acute dose-response determinations, each bird received all doses of each drug on two occasions. Acute drug administrations followed a BCDBBCD design: B represents baseline sessions; C, vehicle control sessions; and D, drug sessions. Methsuximide was dissolved in a solution consisting of four parts propylene glycol and one part ethyl alcohol; mephenytoin was dissolved in dimethyl sulfoxide (DMSO). Testing during pilot trials revealed that neither propylene glycol and ethyl alcohol nor DMSO was behaviorally active. Thus, isotonic saline solution (also found not to be behaviorally active) served as the control vehicle across all birds for both drugs.

After acute dose-response determinations were completed, all subjects received vehicle control injections until percent errors showed no visible trend across three consecutive sessions. At that time, chronic drug administration was begun.

Initially, only three of the four subjects were to be used in the chronic methsuximide phase. It was decided that one of the two
non-naive subjects would be removed from the chronic phase of the present investigation. Thus, MS3 was randomly selected to be removed from this phase.

For subjects receiving methsuximide, the chronic phase was initiated with 10 consecutive daily administrations of 100 mg/kg. This dose was selected because it had obvious behavioral effects in all subjects. However, all subjects receiving these administrations were severely impaired by day 10, necessitating the implementation of baseline conditions until performance again stabilized. Subject MS4 died following these administrations; therefore, subject MS3 was employed during the balance of the study. This subject was placed on baseline conditions along with the others. Once performance was again stabilized for each subject, two control sessions for MS1 and MS2, and six for MS3 immediately preceded 10 consecutive administrations of 50 mg/kg methsuximide, followed by 10 consecutive administrations of 25 mg/kg.

For subjects receiving mephenytoin, the chronic phase was initiated with 10 consecutive daily administrations of 120 mg/kg. This dose, too, was selected because it was behaviorally active in all subjects. Following the tenth consecutive administration, the highest dose administered acutely (i.e., 240 mg/kg) was given to test for behavioral tolerance (this dose produced noteworthy disruptions in performance under acute conditions in two of three subjects), after which five more administrations of 120 mg/kg were given. As a further test for tolerance, a dose of 360 mg/kg was administered following this fifth administration of 120 mg/kg.
RESULTS

The acute and chronic effects of methsuximide and mephenytoin on percent errors and response rates of individual birds are shown in Figures 1 and 2, respectively. These figures depict performance during control sessions, during acute administrations of each dose, during the final session of exposure to all doses administered chronically, and in the case of mephenytoin, during post-chronic exposure to selected doses.

Control data represent performance during each session that immediately preceded drug administration. For methsuximide, control performance is depicted as the mean and standard error of the mean (SEM) across eight vehicle control sessions, one preceding each dose administered (there were two determinations at each dose). Similarly, control performance for mephenytoin represents the mean and SEM across six vehicle control sessions.

Control Performance

In the absence of drug, mean percent errors during control sessions was 11% or below for each bird, with percent errors relatively stable across control sessions. Control response rates varied considerably across birds, but were relatively stable across sessions for each subject. Control percent errors represented in Figures 1 and 2 were calculated to take into account the number of reinforcers earned during each corresponding drug session and represent
Figure 1. The acute and chronic effects of methsuximide on percent errors and response rate for individual subjects. Control data for percent errors are depicted by the unshaded bars in the left panels. Percent errors ([(incorrect responses/incorrect responses + correct responses) x 100] reflect performance until a number of reinforcers equivalent to that obtained during the following drug session was earned. This value (i.e., number of reinforcers earned) is indicated above each drug dose, for the first and second administration, respectively. The standard error of the mean for control performance is represented by the vertical line. Mean percent errors across both acute determinations at each dose is depicted by shaded bars; bars with diagonal lines represent percent errors during the final session of chronic exposure. Sessions where no responding occurred are designated by NR.

The filled circles at C (right frame) indicate the mean rate of responding (total responses/total session time in minutes excluding timeouts and brief stimulus presentations) across control sessions; vertical lines represent the standard error of the mean. Filled circles represent the mean rate of responding during acute determinations; filled triangles, rate of responding during the final chronic session.
Figure 2. The acute and chronic effects of mephenytoin on percent errors and response rate for individual subjects. Details are as described in Figure 1, with the following addition: Percent errors during post-chronic determinations are depicted by a bar filled with small dots (left panel); response rate during these determinations is designated by a filled square (right panel).
performance until a number of reinforcers was earned equal to the number obtained under the immediately following drug session. If, for example, a subject earned 27 reinforcers during the first administration of 50 mg/kg methsuximide, percent errors for the preceding control session would be based only on data recorded until the twenty-seventh reinforcer was earned. The numbers above the control bars in the left panels of Figures 1 and 2 represent the number of reinforcers earned during the first and second administration, respectively.

Acute Effects

In general, acute administrations of both methsuximide and mephenytoin had little effect on percent errors except at doses that substantially decreased the rate of responding. Furthermore, both drugs produced generally dose-dependent decreases in response rate. With methsuximide, rates typically were lowest and percent errors greatest at the highest dose tested (i.e., 100 mg/kg). For all subjects, the lowest dose tested (25 mg/kg) had no disruptive effect on accuracy; higher doses (50 mg/kg, 75 mg/kg) generally produced slight, but not clearly dose-dependent, increases in percent errors relative to control performance. However, subject MSI evidenced substantial behavioral disruption at 75 mg/kg, as well as at 100 mg/kg.

When methsuximide was administered acutely, rate of responding remained above or within one standard error of the control mean at 25 mg/kg for all subjects, at 50 mg/kg for three of four subjects, and at 75 mg/kg for two subjects. Three of four subjects evidenced
response rates substantially below control levels at 100 mg/kg. Only MS3 responded during both administrations of this dose.

As shown in Figure 2, the lowest dose of mephenytoin (60 mg/kg) had little effect on percent errors relative to control performance. The 120 mg/kg dose had no effect on MP1's performance, produced a slight increase in percent errors in MP3, and produced a larger increase in MP2. The highest dose administered acutely (240 mg/kg) substantially increased percent errors in MP1 and MP2, but had little effect in MP3.

Acute administrations of mephenytoin produced, in two of three subjects (MP1, MP2), dose-dependent decreases in response rate, whereas subject MP3 evidenced rate reductions that were not directly dose-dependent. The 240 mg/kg dose of mephenytoin increased errors relative to control values in all subjects; the 120 mg/kg dose did so in two birds (MP2, MP3).

Figure 3 illustrates the within-session effects of methsuximide and mephenytoin. In this figure, control data, which represent the session that immediately preceded drug administration, reflect cumulative errors until a number of reinforcers equivalent to that earned during drug sessions was obtained. As shown in the top four panels, in three of four instances the main effect of methsuximide was to increase the number of errors early in the session, i.e., before 15 reinforcers were obtained. Thereafter, the number of errors per reinforcer typically approximated those obtained during control sessions. For one subject (MS1), the dose displayed in this figure did not affect the early within-session distribution of errors, although a
Figure 3. Within-session distribution of errors (cumulative errors across blocks of three reinforcers) during selected drug and control sessions. Drug sessions represent the first administration of a dose that affected accuracy (i.e., percent errors). Control data represent performance during the session immediately preceding drug administration until a number of reinforcers equivalent to that obtained during the following drug session was earned.
moderate increase in errors was observed during the later blocks of reinforcers.

As seen in the lower three panels of Figure 3, for subjects MP1 and MP2 the error-increasing effects of mephenytoin were most evident early in the session. In the case of MP1, the single data point for the drug condition represents the second determination of 240 mg/kg, during which only one reinforcer was obtained. This particular datum is presented since it represents the only dose which increased percent errors relative to control performance; the first determination of this dose resulted in no responding by this subject. Subject MP2 evidenced a dramatic increase in errors during early acquisition relative to control; thereafter, the number of errors per reinforcer approximated values obtained during control session. For MP3, the dose displayed in this figure increased the percent errors above control, and affected the within-session distribution of errors until 30 reinforcers were obtained. The number of errors per reinforcer made thereafter was similar to control performance. Thus, the effects of mephenytoin on the within-session distribution of errors, like those of methsuximide, were most evident early in the session, that is, during the acquisition of the four-response sequence.

Chronic Effects

As depicted in Figure 1, tolerance did not develop to the behavioral effects of methsuximide. The absence of tolerance to methsuximide is shown by the increase in percent errors in two of three subjects following chronic exposure to 50 mg/kg, the decrease in response
rates at all doses tested across all subjects, and in the complete cessation of responding observed during sessions when subjects were chronically exposed to 100 mg/kg. These data suggest that methsuximide, at daily doses of 50 and 100 mg/kg, accumulated in the body at a higher rate than it was eliminated. Chronic exposure to 25 mg/kg methsuximide produced less evidence of accumulation. Chronic exposure to this dose had little effect on percent errors, but in all subjects response rate was substantially reduced relative to acute values. As previously noted, one subject (MS4) became ill and died following chronic exposure to 100 mg/kg methsuximide; a second became ill and lost a substantial amount of weight, but recovered when drug treatment ended. This further suggests that methsuximide accumulated in the body with daily exposure to 100 mg/kg.

Tolerance appeared to develop to the behavioral effects of mephenytoin. In all subjects, percent errors during the final session of chronic exposure to 120 mg/kg of this drug was lower than the value obtained with acute administration. Moreover, subjects responded and made relatively few errors when given 240 or 360 mg/kg post-chronically, although acute administrations of 240 mg/kg strongly suppressed responding and, in two subjects, increased errors relative to control values. Furthermore, response rates across all subjects were higher during the post-chronic determination at 240 mg/kg than during acute dose-response determinations at this dose. For two of three subjects, post-chronic determination at 360 mg/kg also revealed percent errors lower than those obtained during acute testing at 240 mg/kg and 120 mg/kg, and response rates higher than those obtained during acute testing of 240 mg/kg.
DISCUSSION

Learning impairment is recognized as a potentially serious behavioral side effect of antiepilepsy medications. The present findings lend additional support to the growing body of preclinical and clinical evidence suggesting that the majority of anticonvulsants may produce this undesirable action (Gibbs et al., 1982; Paule & Killam, 1979; Poling & Picker, 1987; Stores, 1975; Trimble & Reynolds, 1976). In the present study, acute administrations of both methsuximide and mephenytoin at certain doses substantially increased overall percent errors under the repeated acquisition procedure. This typically occurred at doses that substantially reduced the rate of responding and number of reinforcers earned. When response rate was little affected by drug and a subject earned the maximum number of reinforcers possible during a given session (i.e., 60), percent errors approximated performance under control conditions.

Drug-induced changes in overall percent errors alone, however, do not necessarily indicate learning impairment. As Thompson and Moerschbaecher (1979) have emphasized, drugs that truly disrupt learning affect the within-session distribution of errors under the repeated acquisition procedure. A within-session analysis of the distribution of errors (i.e., errors cumulated across reinforcers) in the present study revealed that the main effect of methsuximide and mephenytoin was to increase errors during early acquisition (i.e., before the procurement of 15 or fewer food deliveries),
suggesting that these drugs actually were interfering with learning. With repeated exposure to the 4-response sequence, the number of errors per reinforcer gradually decreased, approximating performance during corresponding control sessions.

This finding is consistent with a wealth of data showing that behavior under strong stimulus control is less disrupted by drugs than is behavior under weaker stimulus control (Poling, 1986). During acquisition, the correct response in the presence of each stimulus is gradually acquired through differential reinforcement. Incorrect responses are followed by a timeout during which all the lights in the chamber are darkened and responding has no programmed consequences. Correct responses, in contrast, are followed by either a stimulus change correlated with the next component in the chain (which functions as conditioned reinforcement since it represents a betterment in terms of nearness to reinforcement), or in the case of the fifth correct response in the presence of the red key light, unconditioned reinforcement in the form of 3-sec access to grain. Stimulus control (learning) occurs and increases across the course of the session.

Drug effects are greatest early in the session, when learning is occurring and stimulus control is weak. Later in the session, stimulus control increases and drug effects are attenuated. From this perspective, the general finding that drugs disrupt learning more than the performance of well learned behaviors (Thompson & Moerschbaecher, 1979) can be construed as a special case of degree of stimulus control modulating drug action.

Understanding the mechanisms that control behavior in the absence
of drug is essential to determining a drug's behavioral mechanism of action (Thompson, 1981). In the case of the repeated acquisition procedure, the four-response chain is apparently controlled by exteroceptive stimuli with discriminative and reinforcing functions. Across many sessions, in the absence of drug, a characteristic pattern of acquisition develops and percent errors per session becomes relatively stable. The typical pattern consists of many errors early in the session, with fewer errors as the session progresses, indicating that repeated exposure to the environmental contingencies establishes stimulus control over the subject's behavior. Before stimulus control is well established, many errors are made, learning is occurring, and drug effects are maximal. Once stimulus control is well established, the subject makes few if any errors, the sequence has been learned, and drug effects are minimal.

Poling and his colleagues have previously examined the behavioral effects of ethosuximide and phenytoin, which are similar chemically to methsuximide and mephenytoin. Ethosuximide and methsuximide belong to the class of anticonvulsants known as succinimides, whereas phenytoin and mephenytoin are hydantoins. Picker and Poling (1984) and Poling et al. (1986) investigated the effects of ethosuximide and phenytoin in pigeons performing under a repeated acquisition procedure. Given acutely, ethosuximide (40-160 mg/kg) inconsistently increased errors across the range of doses studied, had little effect on the within-session distribution of errors, and produced generally dose-dependent decreases in response rate. Phenytoin (2.5-15.0 mg/kg) substantially increased errors, disrupted accuracy early in the
session, and produced dose-dependent decreases in rate of responding. Poling et al. (1986) also reported the results of chronic exposure to these agents. Their chronic regimen consisted of 10-12 consecutive sessions at the lowest dose, 10-12 consecutive sessions at the middle dose, and finally, 30 consecutive sessions at the highest dose. Under these conditions, appreciable tolerance developed to the behavioral effects of both drugs.

In the present investigation, acute administrations of methsuximide had little effect on percent errors except at doses that substantially reduced the rate of responding. In addition, a within-session analysis revealed that errors were most evident during early acquisition of the sequence. The fact that a dose-dependent reduction in response rate occurred as a result of methsuximide administration is consistent with the findings reported by Picker and Poling (1984) for ethosuximide. Ethosuximide, however, produced weak and inconsistent effects on accuracy (percent errors) at all doses tested, but at least one dose (i.e., 100 mg/kg) of methsuximide substantially disrupted accuracy in all subjects.

Chronic exposure to ethosuximide resulted in tolerance to the accuracy-reducing effects, and partial tolerance (i.e., a diminished drug effect with repeated exposure, without complete return to non-drug response levels) to its rate-reducing effects. In contrast, tolerance did not develop to either of these behavioral effects of methsuximide. Given that chronic exposure produces data most relevant to clinical use (i.e., humans receive anticonvulsants on a chronic basis), on the basis of the present data and those of earlier
nonhuman investigations, it appears that ethosuximide is less likely than methsuximide to impair learning.

The present investigation revealed that appreciable tolerance developed to the accuracy-reducing and rate-reducing effects of mephenytoin. These data are similar to those reported by Poling et al. (1986) for phenytoin. Undesirable physiological side effects of mephenytoin historically have limited its clinical applications regardless of its behavioral actions. In recent years, however, the clinical use of mephenytoin alone or in combination with other agents has been reappraised. Troupin, Ojemann, and Dodrill (1976), for example, reported that of 93 subjects, approximately 75% evidenced a reduction in seizure frequency or complete seizure control while taking mephenytoin. Many of the objective side effects of cerebellar origin seen with phenytoin were rarely seen, and hirsutism, gingival hypertrophy, and peripheral neuropathies were absent. Performance on psychological tests of cognitive-attentional skills also showed a modest improvement.

In general, the results of the present investigation provide additional information on the behavioral actions of antiepilepsy medications. Although anticonvulsants from the same chemical class often possess similar therapeutic actions (i.e., control the same types of seizures), their behavioral and physiological side effects may differ markedly. Because well-controlled research with epileptic patients is difficult or impossible to conduct, research with non-humans may prove useful in detecting these untoward reactions. Results of such studies must be interpreted with due caution, for it
is not clear whether findings with nonepileptic pigeons generalize fully to epileptic humans. Behavioral pharmacologists assume, however, that drug effects are similar across species, and this assumption is empirically well supported. As Poling and Picker (1986) noted, "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). The present data add, perhaps, a modicum to that accounting.
BIBLIOGRAPHY


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