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Effects of Withdrawing Diphenylhydantoin (Dilantin) on Matching to Sample Performance in Mentally Retarded Persons

Vicky June Davis
Western Michigan University

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EFFECTS OF WITHDRAWING DIPHENYLHYDANTOIN
(DILANTIN) ON MATCHING TO SAMPLE PERFORMANCE IN
MENTALLY RETARDED PERSONS

by

Vicky June Davis

A Thesis
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Faculty of The Graduate College
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requirements for the
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Western Michigan University
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EFFECTS OF WITHDRAWING DIPHENYLHYDANTOIN (DILANTIN) ON MATCHING TO SAMPLE PERFORMANCE IN MENTALLY RETARDED PERSONS

Vicky June Davis, M.A.
Western Michigan University, 1980

The present study was designed to examine the effects of gradual DPH withdrawal on the matching to sample performance of three mentally retarded persons. The percentage of correct responses per session served as the dependent variable and the sample and comparison stimuli were red, green, and blue illuminations of translucent response windows. The results showed that doses of diphenylhydantoin considerably lower than the suggested optimum therapeutic level can impair the performance of mentally retarded individuals on a simple discrimination task. As doses were reduced for each subject, there were increases in the percentage of correct responding with the highest percentage correct being obtained after, and only after, the 0 mg dose was reached. The results are discussed in terms of generality, the matching to sample procedure being well suited to the study of drug effects with severely mentally retarded individuals, and implications for habilitation.
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CHAPTER I

INTRODUCTION

Diphenylhydantoin (Dilantin-DPH) has been the medication of choice for the control of seizures with all types of populations since its introduction by Merritt and Putnam in 1938. There has also been considerable use of this drug with non-epileptics including children with behavioral, emotional, and learning problems, delinquents, neurotic adult outpatients, and normal adults.

DPH is one of three synthetic hydantoins used in the treatment of major motor (Grand mal) and psychomotor (temporal lobe) epilepsy. Ethotoin (Peganone) and mephenytoin (Mesantoin) are the other hydantoins but are used considerably less than DPH because of their greater likelihood of toxicity and other side effects. As an antiepileptic, DPH appears to act on the motor cortex to stabilize, rather than raise, normal seizure thresholds and prevent the spread of seizure activity rather than abolish the primary focus of seizure discharges. Depression of central nervous system activity is not usually reported. Pharmacokinetically, DPH is well absorbed by mouth, metabolized by the liver, and is primarily excreted in the urine (Rall and Schleifer, 1980).

Despite the wide use of DPH, only recently have studies begun to examine its effects on learning and performance. The results of these studies which have used a variety of non-retarded subjects and procedures, are conflicting. Haward (1970, 1973) and Smith and Lowrey
(1972, 1975) report an enhancement of learning and performance as measured by norm-referenced IQ test scores. However, Rosen (1968), Idenström, Schalling, Carlquist, and Sjöqvist (1972), Dekaban and Lehman (1975), Dodrill (1975), Mathews and Harley (1975), Stores and Hart (1976), and Trimble (1979) report an impairment of learning and performance on a variety of tasks including free recall, reaction time, reading, and vigilance. Decreases in norm-referenced IQ scores were also reported by these authors.

While methodological differences and problems make it difficult to compare the findings of these studies, objective measures of learning and performance as criteria for evaluating drug effects are well established (e.g., Sprague and Werry, 1971, 1974). However, only one study examining the effects of antiepileptic drugs on learning and performance with the mentally retarded could be found (i.e., Goldberg and Kurland, 1970). This is surprising, since mental retardation usually is defined with some reference to inadequate or slow learning and antiepilepsy drugs are used with this population. It is currently estimated that approximately 190,000 mentally retarded persons reside in public institutions (e.g., Breuning and Poling, in press). Of these 190,000 persons, approximately 65,000 are receiving an antiepilepsy drug with DPH accounting for approximately 45% of this total (e.g., Sprague, 1977; Pulman, Pook, and Singh, 1979). A recent survey of drug use with mentally retarded persons in community foster-group homes found that approximately 40% of these individuals received DPH alone or in combination
Goldberg and Kurland (1970) compared the effects of DPH and placebo on three performance measures with 47 children reported as having cultural-familial retardation. No additional assessment information was provided. The performance measures were scores on the Wechsler Intelligence Scale for Children (WISC) and Porteus Mazes, and improvement on an unstructured nonverbal task. The results showed no overall statistical differences between DPH and placebo on any of the three measures.

A tempting interpretation of Goldberg and Kurland's (1970) results is that DPH does not significantly affect learning and performance in mentally retarded persons. However, several investigators (e.g., Sprague and Werry, 1971; Sulzbacher, 1973; and Breuning and Davidson, in press) have demonstrated that norm-referenced IQ tests and unstructured tasks are generally insensitive to drug effects. Thus, before such an interpretation can be accepted, a more sensitive measure of drug effects must be employed.

One measure of performance demonstrated to be sensitive to drug effects is referred to as matching to sample. This is a discrimination task described in detail by Cumming and Berryman (1965). In the matching to sample procedure, the subject is presented a sample stimulus. A response to this stimulus results in the termination of the stimulus and the immediate (zero delay) presentation of two comparison stimuli. A response to the comparison stimulus that matches the sample stimulus is reinforced; a response to the other comparison
stimulus is not reinforced but terminates the trial (and, in some studies, initiates a brief timeout). The sensitivity of this procedure to drug effects has been established in both the human and nonhuman literature (e.g., Wysocki, Fuqua, Davis, and Breuning, in press; Cumming and Berryman, 1965).

The present study was designed to examine the effects of gradual DPH withdrawal on the matching to sample performance of three mentally retarded persons. The percentage of correct responses per session served as the dependent variable and the sample and comparison stimuli were red, green, and blue illuminations of translucent response windows.
CHAPTER II

METHOD

Subjects

Three institutionalized, mentally retarded persons served as subjects in the study. Each subject had been identified by a team consisting of a physician, nurse, and psychologist for gradual and systematic withdrawal from diphenylhydantoin (DPH). Each subject had been receiving DPH for at least three consecutive years. The absence of observed seizures for 3 years or more was the criteria for withdrawal. The subjects were receiving no other anticonvulsant or psychotropic medications. Informed consent was obtained for each subject's participation.

Subject D was a 27 year old female receiving 100 mg of DPH. The DPH/serum level was 3.0 ug/ml. Her waking EEG consisted of high voltage 10 per second waveform activity in all areas. During drowsiness and sleep, frequent spike seizure discharges were recorded in the left and right anterior temporal and mid-temporal areas.

Subject L was a 23 year old female receiving 300 mg (100 TID) of DPH. The DPH/serum level was 4.1 ug/ml. Her waking EEG consisted of medium voltage 10 per second waveform activity in all areas. There were no focal abnormalities nor seizure discharges. Normal activity was recorded during drowsiness and sleep.

Subject E was a 16 year old male receiving 300 mg (100 TID)
of DPH. The DPH/serum level was 3.5 ug/ml. His waking EEG consisted of medium voltage 6-to-8 per second waveform activity. During drowsiness and sleep, moderately frequent 14 and 6 per second positive spike seizure discharges were recorded in the left and right temporal and occipital areas.

Table 1 summarizes the above data and provides additional demographic information concerning IQ, DPH dose prior to withdrawal, mg/kg dose, and months on this dose.

**Setting and Apparatus**

Sessions were conducted in a room measuring approximately 3.0 m by 7.1 m. The room had a 1.2 m by 0.9 m one-way observation window mounted within one of the sidewalls and contained a table and a chair with an intelligence panel mounted on top of the table. The intelligence panel consisted of a horizontal array of three 15.2 cm square plexiglas response windows. A reinforcement dispenser was mounted 10.0 cm below the center window. Projection equipment in the adjacent room provided capabilities for illuminating a 5.0 cm square in the center of each of the three windows with any of three colors: red (640 nm), green (530 nm), or blue (480 nm). Reinforcers consisted of small chocolate or peanut candy pieces. Stimulus presentations, experimental contingencies, and data collection were controlled automatically by solid state and electromechanical programming equipment located in the adjacent room.
Table I. Baseline age, sex, IQ, DPH dose, DPH/serum level, and months on initial DPH dose for each subject.
### TABLE I

**BASELINE AGE, SEX, IQ, DPH DOSE, DPH/SERUM LEVEL, AND MONTHS ON INITIAL DPH DOSE FOR EACH SUBJECT**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (Years)</th>
<th>Sex</th>
<th>IQ</th>
<th>DPH Dose (mg)</th>
<th>DPH Dose (mg/kg)</th>
<th>DPH/Serum Level (ug/ml)</th>
<th>Months on Initial DPH Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>27</td>
<td>F</td>
<td>30</td>
<td>100</td>
<td>2.14</td>
<td>3.0</td>
<td>39</td>
</tr>
<tr>
<td>L</td>
<td>23</td>
<td>F</td>
<td>34</td>
<td>300</td>
<td>5.19</td>
<td>4.1</td>
<td>4</td>
</tr>
<tr>
<td>E</td>
<td>16</td>
<td>M</td>
<td>47</td>
<td>300</td>
<td>5.28</td>
<td>3.5</td>
<td>38</td>
</tr>
</tbody>
</table>

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Procedure

Each subject received oral administrations of DPH from the program nurse. Subject D received DPH in one daily dose and Subjects L and E received three equal daily doses. Daily baseline doses for D, L, and E were 100 mg, 300 (100 mg TID), and 300 mg (100 mg TID), respectively.

A zero delay matching to sample procedure was used throughout the study (pretraining and experiment proper). At the start of each session a subject was seated in front of the intelligence panel and the center response window was illuminated with one of the three colors (sample stimulus). Pressing the illuminated center window terminated its illumination and simultaneously resulted in the illumination of the two side windows (comparison stimuli). One of the side windows was illuminated with the same color (matching stimulus) as the center window (sample stimulus) and the other was illuminated with a different color (non-matching stimulus). Color assignments for each window were randomized with each color appearing equally often as sample, matching, and non-matching stimuli.

A response to the matching stimulus resulted in the termination of its illumination, delivery of one reinforcer, and a 0.5 sec, 1000 hz tone (40.0 db, re 20 uN/m²). A response to the non-matching stimulus or no response within 30 sec terminated the illumination in both side windows for a 10 sec timeout prior to the onset of the next trial (i.e., illumination of the center window). A failure to re-
spond within 30 sec was counted as an error. Five sec after reinforcement or 10 sec after an incorrect response (error), the center window was illuminated to begin the next trial. Each trial on which an incorrect response occurred was repeated until the subject emitted the correct response. Percentage correct responses per session (correct responses/total responses X 100) was the dependent variable.

Each subject received two or three sessions per week with each session consisting of 30 trials. Session times were scheduled either between 8:00-8:30 a.m. or 3:00-4:00 p.m. The number of sessions per week and the times of the sessions occasionally varied because of special habilitative events or illness.

The first three sessions were pretraining sessions. The matching to sample procedure described above was followed except that the subjects were given vocal and physical assistance. Across these sessions, the amount of assistance was gradually faded out and by the end of the third session each subject responded independently.

The fourth session began the experiment proper, in which DPH doses were systematically reduced following a multiple-baseline-across-subjects design (Bar, Wolf, and Risley, 1968). Subject D received one dose reduction (100 mg to 0 mg) while Subjects L and E received two reductions (300 mg to 150 mg to 0 mg). The number of daily DPH administrations was not altered as the dose was reduced; an inactive placebo was administered when the 0 mg dose was reached. The matching to sample performance of each subject was assessed at all dose levels, as described above. The number of sessions in which the
matching to sample performance of each person was tested at each dose level is shown later in Figure 1. DPH/serum levels and EEG assessments were completed prior to baseline (Session 1) and the final dose reduction (Sessions 13, 42, and 55 for Subjects D, L, and E, respectively). Subjects L and E received an additional DPH/serum level and EEG assessment four days after the onset of the 150 mg dose (Sessions 22 and 30, respectively). Routine Regional Center seizure monitoring procedures were in effect throughout the study. Double-blind procedures were used, as neither the ward staff nor the subjects were aware of the DPH dose or whether a placebo was being used.
CHAPTER III

RESULTS

Figure 1 shows the percentage of correct responding per session for each subject at each DPH dose. Figure 2 depicts the highest percentage of correct responding within a single session reached at each DPH dose by each of the three subjects.

During the baseline condition, when Subjects D, L, and E received 100 mg, 300 mg, and 300 mg, respectively, the performance of each subject was rather variable. Subject D's percentage of correct responding ranged from 20% to 50% with considerable variability. Subject L's percentage of correct responding ranged from 43% to 77%. Again, responding was quite variable. Subject E's percentage of correct responding ranged from 27% to 67% and showed little variability across the last four sessions.

The first dose reduction for Subjects L and E was from 300 mg to 150 mg. For both subjects, this reduction failed to strongly affect performance. Subject L's percentage of correct responding at the 150 mg dose ranged from 43% to 77% and was very similar to her responding under the 300 mg dose, except for an eventual decrease in variability. Subject E's percentage of correct responding ranged from 40% to 87% at the 150 mg dose, and some evidence of a dose reduction effect was present. However, percent correct responding at the 150 mg dose showed a transient increase but did not remain at a level consistently different from the ones obtained at the preceding 300 mg dose.
Figure 1. The percentage of correct responses per session at each dose of diphenylhydantoin for the three subjects.
Figure 2. The highest percentage of correct responses at each dose of diphenylhydantoin for the three subjects.
The highest percentage of correct responding for each subject was obtained at the 0 mg dose. Across sessions, Subject D's percentage of correct responding ranged from 10% to 73%. Percentage correct responding decreased during the second session at 0 mg, then increased across sessions, reaching 73% by the eighth session and 67% by the ninth session. At this point, Subject D was placed in a group home and her participation in the study ended. Subject L's percentage of correct responding ranged from 53% to 90%. Responding on the first four 0 mg sessions was within the range obtained on the last seven 150 mg sessions. Responding then began to gradually increase and peaked at 90% in four sessions. Responding on the last two sessions was within 3% of the peak. Subject E's percentage of correct responding ranged from 37% to 97%. Responding decreased on the first 0 mg session, followed by a gradual increase in responding across the next nine sessions. Responding peaked at this point and was within 7% of this peak on the last three 0 mg sessions. Subjects L and E completed their participation in the study at their respective points because of numerous Regional Center changes (e.g., ward reassignments, school schedule changes, and rescheduling of habilitative programs).

As stated earlier, at the onset of the study Subject D received 100 mg DPH daily, while Subjects L and E each received 300 mg. Their DPH/serum levels at this time were 3.0 ug/ml, 4.1 ug/ml, and 3.5 ug/ml respectively. At the end of the 100 mg dose (just prior to onset of the 0 mg dose), Subject D's DPH/serum level was 2.8 ug/ml (Session 13). Four days after the onset of the 150 mg dose, the DPH/serum levels of
Subjects L and E were 2.6 ug/ml (Session 22) and 1.6 ug/ml (Session 30) respectively. At the end of the 150 mg dose (just prior to onset of the 0 mg dose) Subjects L and E had levels of 2.2 ug/ml (Session 42) and 1.9 ug/ml (Session 55). These values indicate that DPH/serum levels were lawfully related to the amount of DPH ingested, although somewhat variable across subjects. There were no EEG changes for any subject following any of the DPH dose reductions.
CHAPTER IV
DISCUSSION

The results showed that doses of diphenylhydantoin considerably lower than the suggested optimum therapeutic level (10-20 ug/ml; Rall and Schleifer, 1980) can impair the performance of mentally retarded individuals on a simple discrimination task. As doses were reduced for each subject, there were increases in the percentage of correct responding with the highest percentage correct being obtained after, and only after, the 0 mg dose was reached.

The present results do not seem to be due to practice effects. None of the subjects showed any substantial evidence of improvement at their initial drug dose despite a varying number of sessions (12, 19, and 27 respectively for D, L, and E). Subject L also failed to show evidence of continued improvement across her 50% dose reduction, an additional 22 sessions. Finally, Subject E showed an initial increase followed by a decrease in performance across his 50% dose reduction, a trend not typical of a practice effect.

There are several points pertaining to the data and the procedure in general that warrant discussion. First, there is the unexpected finding that all three subjects had a considerable number of sessions where the percentage of correct responding was below 50%, the "chance" level that would result from random responding. In fact, percentage correct responding by Subject D while receiving DPH only reached 50% once. This finding, as well as the marked variability in responding
across sessions when DPH was given, appears to be due to response perseverance. While receiving DPH, each subject often emitted several consecutive responses (often 8 or 9) to the same side response window regardless of whether the response was reinforced. Such response perseveration was almost nonexistent (never more than three consecutive incorrect responses to the same window) at the 0 mg dose.

Second, Subject E showed an initial increase in percentage correct responding following the onset of the 150 mg dose. This trend lasted for six sessions and was followed by a gradual return to the level of responding obtained at the 300 mg dose. The reasons for this are unclear; however, his DPH/serum level was slightly higher at the end of this condition than at the start (1.6 ug/ml v. 1.9 ug/ml). Whether this seemingly small increase was responsible for the decrease in performance cannot be answered with the present data. It is possible that DPH/serum – performance relationships are dependent upon idiosyncratic thresholds; this interesting and possibly important issue demands future research.

Third, the matching to sample procedure appears well suited to the study of drug effects with severely mentally retarded individuals. Minimal physical-motor skills were required by the subjects and the present results indicate that the procedure, in apparent contrast to those sometimes employed (e.g., Goldberg and Kurland, 1970), was sensitive to dose changes. This is consistent with the findings of a recent study by Wysocki, Fuqua, Davis, and Breuning (in press).

Despite the consistent effects across subjects, generalization to other mentally retarded individuals receiving DPH and to non-mentally
retarded individuals receiving DPH must be with extreme caution. The subjects in the present study are probably not representative of most "epileptics", for no seizures had ever been observed in the subjects. It is possible that despite some EEG abnormalities, they had been inappropriately placed or maintained on DPH. Individuals with an active seizure disorder, whether mentally retarded or not, may show a different pattern of responding in conjunction with DPH changes.

While the subjects in the present study are perhaps not typical of most epileptics receiving DPH, there is a large number of mentally retarded individuals receiving DPH of whom they are representative. As stated earlier, 40% to 45% of the mentally retarded in institutions and community foster-group homes are receiving DPH. Recent estimates indicate that observed seizures have not been documented in between 10% to 50% of these individuals (e.g., Corbett, Harris, and Robinson, 1975; Kaufman, and Katz-Garris, 1979), with the best estimate being approximately 28% (Davis, Cullari, and Breuning, in press). It is not unreasonable to generalize the present findings to these individuals nor to suggest that many of them are experiencing an unnecessary drug-induced impairment in performance.

If, as many have suggested (e.g., Skinner, 1938; Sidman, 1960), matching to sample reflects a behavioral process common to many habilitative programs used with the mentally retarded, there may be serious legal implications. For example, Standard 22 of the "Minimum Constitutional Standards for the Adequate Habilitation of the Mentally Retarded" that resulted from Wyatt v. Stickney (1972) states that:
Residents shall have the right to be free from unnecessary or excessive medication...medication shall not be used in quantities that interfere with a resident's habilitative program (page 400).

Finally, it is important to note that throughout the study none of the subjects showed evidence of a clinical seizure. Nor have they done so from the end of the study to the time of this writing—now more than 75 days. This certainly does not indicate that all mentally retarded individuals receiving DPH but remaining seizure free for an extended period of time could be successfully titrated off of the drug. Probably some could not. Nonetheless, given the possible impairment of adaptive behavioral processes that may be associated with unnecessary diphenylhydantoin administration, an attempt to decrease or eliminate the drug is a reasonable venture.
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