Relationship Between the Plasma Level of Diphenylhydantoin Sodium and Its Cardiac Antiarrhythmic Effects

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SUMMARY
The effect of diphenylhydantoin sodium (DPH, Dilantin) on a variety of arrhythmias was studied in relation to its plasma levels. DPH was administered in one of three ways: (1) multiple intravenous doses, (2) single intravenous doses, and (3) oral doses. Ventricular arrhythmias occurring in many clinical conditions and atrial tachycardia, particularly if caused by digitalis excess, responded well to treatment with DPH. Three fourths of the responsive arrhythmias were abolished at plasma levels of DPH of 10 to 18 μg/ml. In most cases a critical, effective plasma level could be demonstrated; this level had to be exceeded in order to suppress the arrhythmia being treated.

A method of rapidly effective oral therapy of arrhythmias with diphenylhydantoin is described, and a method of transition from intravenous to oral therapy is demonstrated.

The antiarrhythmic action of diphenylhydantoin was accompanied by neither depression of sinoatrial nodal activity nor atrioventricular or intraventricular conduction disturbances, but was accompanied by a shortening of the Q-T interval. Hypotension accompanying the intravenous use of this drug was minimized by administration of the full dose in increments.

Additional Indexing Words:
Digitalis  Electrocardiographic effects  Intraventricular conduction
Electrical systole

Although the antiarrhythmic action of diphenylhydantoin (DPH) has been demonstrated in both animals and man, opinions differ regarding the clinical usefulness of this drug. For example, Conn found DPH effective in abolishing atrial and ventricular arrhythmias in the presence or absence of digitalis; Bernstein and associates found it useful in managing recurrent arrhythmias which were unrelated to digitalis therapy, while Rosen and associates had little success with DPH except in arrhythmias that had developed in patients receiving digitalis. These divergent results have arisen in part from differences in dosage levels and routes of administration. Hence, the purpose of the present study was to relate the antiarrhythmic action of DPH to its concentration in the plasma.

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Specifically, the study had four objectives: (1) to define the time course of the plasma concentration after DPH had been administered by a single intravenous injection, by multiple intravenous injections, or by multiple oral doses; (2) to examine the relation of the plasma level to the effect of DPH on various arrhythmias; (3) to inquire whether DPH altered the systemic arterial pressure or the electrocardiogram; and (4) to establish the incidence of undesirable actions of intravenously administered DPH.

Methods

Although a few of the patients studied were thought to have normal hearts, the majority had some form of cardiovascular disease. A total of 93 patients were studied: 25 had sustained a recent myocardial infarction, 14 had undergone open heart surgery for aortic or mitral valve replacement, and eight had sustained a cardiac arrest. Of the total of 93 patients, 28 were receiving digitalis and seven of those were thought to have signs of digitalis excess.

The sole criterion for selection was the presence of an arrhythmia. The abnormal rhythms included atrial premature contractions, atrial tachycardia, atrial flutter, atrial fibrillation, A-V junctional (nodal) premature contractions, A-V junctional (nodal) tachycardias, ventricular premature contractions, ventricular tachycardia, and complex arrhythmias.

To test the relationship of plasma level, dosage, and mode of administration, the patients were divided into three groups. Group I comprised 68 patients who received multiple intravenous injections of 50 or 100 mg of DPH every 5 min. The DPH was dissolved in the commercial diluent (40% propylene glycol and 10% ethanol in water, pH 12). Each dose of DPH was followed by an injection of sterile saline to prevent pain and inflammation at the injection site. Blood samples for plasma DPH determination were drawn from the arm not used for injection. Successive doses of DPH were given every 5 min until the arrhythmia was abolished, until 1,000 mg had been given, or until undesirable effects appeared. If the arrhythmia disappeared, drug administration was halted; if the arrhythmia reappeared, drug administration was resumed in the same manner until the arrhythmia was once again abolished. This sequence was often repeated several times. Throughout the study blood samples and an ECG were obtained every 5 min and the arterial blood pressure was measured every 5 or 10 min.

Group II comprised 15 patients who received a single intravenous dose of 300 mg of DPH. Samples for plasma DPH determination and an ECG were obtained at 5, 10, 20, 40, and 60 min and 2, 4, 8, 12 and 24 hr after injection to measure the peak plasma DPH level obtained, the time course of its disappearance, and the effect obtained on the arrhythmia.

Group III comprised 10 patients who received oral doses of DPH, administered every 6 hr. The dosage schedule (total daily dose) was: day 1, 1,000 mg; day 2, 500 mg; day 3, 500 mg; and 400 mg/day thereafter. During preliminary studies, several patients were treated from the outset with 400 mg/day. DPH plasma levels were determined after the second and fourth doses each day for 4 days, then once daily in the morning. Continuous electrocardiographic monitoring was instituted for the duration of the study to relate the course of the arrhythmia in these patients to drug dosage and plasma level.

Several patients of group III were given DPH intravenously on the first day to abolish an arrhythmia; the remainder of the day's 1,000-mg dose was given orally; and oral maintenance was continued. If the arrhythmia recurred later in the treatment course, a blood sample for determination of plasma DPH was obtained, and DPH was administered intravenously in 100-mg increments every 5 min until the arrhythmia was abolished. A second blood sample was then obtained, and oral maintenance was continued. In most cases use of the drug was discontinued after 3 to 5 weeks. DPH plasma level and the electrocardiogram were then followed to determine the time course of DPH decline and whether or not the arrhythmia would recur.

Determination of Plasma Diphenylhydantoin

Blood was collected in tubes containing ethylenediamine tetraacetate (EDTA) as an anticoagulant. Plasma was separated by centrifugation at 5,000 rpm for 10 min, then stored at 4 C. DPH concentration was determined by a modification of the technique of Dill and associates. This entailed extracting DPH with chloroform, washing the extract with borate buffer to remove other drugs such as barbiturates and salicylates, and diazotizing the DPH residue with Bratton-Marshall reagents. The concentration of DPH was then determined by ultraviolet spectrometry, using standards and blanks prepared with the patient's plasma.

The borate buffer removes 85 to 95% of interfering substances such as barbiturates or salicylates. None of these patients was receiving primidone which interferes with DPH determination and is not extracted by borate buffer. The purity of the DPH extract was periodically determined by paper chromatography using Armstrong solvent systems.
Table 1

Arrhythmias Studied: Results of Treatment of the Sixty-eight Patients in Group I

<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>No. of cases</th>
<th>Abolishment of arrhythmia</th>
<th>Plasma level (µg/ml)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>12</td>
<td>0</td>
<td>15-33</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>5</td>
<td>0</td>
<td>19-30</td>
</tr>
<tr>
<td>Atrial premature systoles</td>
<td>5</td>
<td>0</td>
<td>5-24</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>9</td>
<td>7</td>
<td>12-23</td>
</tr>
<tr>
<td>A-V junctional premature systoles</td>
<td>4</td>
<td>0</td>
<td>21-32</td>
</tr>
<tr>
<td>A-V dissociation with interference</td>
<td>6</td>
<td>0</td>
<td>15-33</td>
</tr>
<tr>
<td>Ventricular premature systoles</td>
<td>26</td>
<td>26</td>
<td>4-24</td>
</tr>
<tr>
<td>Ventricular parasystole</td>
<td>1</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>68</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Fifty to 100 mg of DPH was given intravenously every 5 min until: (1) the arrhythmia was abolished; (2) 1,000 mg had been given; or (3) undesirable effects appeared.

†Range of plasma level given represents either (1) the level at which the arrhythmia was abolished or (2) the highest level achieved in those patients who failed to respond to the drug.

The sensitivity of this technique is such that 0.5 µg/ml can be detected; concentrations of 1.0 µg/ml and higher can be measured reproducibly. The reproducibility of measurement was evaluated with DPH standards over a wide range of concentrations; the standard deviation at a concentration of 3.0 µg/ml was 0.12, at 5.0 µg/ml was 0.21, at 10.0 µg/ml was 0.24, and at 15.0 µg/ml was 0.31 µg/ml.

Results

Response of the Patients in Group I

Data obtained from the 68 patients in group I are summarized in table 1. The DPH plasma levels in column four represent either the level at which arrhythmia conversion occurred or the highest level attained in unresponsive patients. The effectiveness of DPH in abolishing most atrial arrhythmias was low despite the very high plasma levels in almost every case. Atrial premature systoles in one case showed a marked decrease and in another a moderate decrease in frequency, but in no instance were atrial premature contractions abolished. Seven of nine atrial tachycardias were abolished by DPH at moderate plasma levels (8 to 16 µg/ml). In the two unresponsive cases, 1,000 mg was administered and plasma levels of 20 to 23 µg/ml were achieved. The tachycardia in three of the seven patients with atrial tachycardia that converted was presumed to be due to digitalis excess; the other four patients were not receiving digitalis.

Six patients had atrioventricular dissociation, with interference. An atrioventricular junctional focus fired faster than the independent sinoatrial pacemaker and therefore controlled the ventricles; the QRS was normal. Sinoatrial capture of the ventricles occurred at expected times demonstrating that atrioventricular block was absent or minimal. The patients exhibiting these arrhythmias had myocardial infarction (two patients), recent open heart surgery (two), or probable digitalis excess (two). Administration of DPH had little or no effect on this rhythm.

The success rate in treating frequent ventricular premature contractions was high. Twenty-six of 27 attempts were successful. In three cases the ventricular premature contractions disappeared at very low plasma levels. A substantial proportion of these arrhythmias had been persistent, despite treatment with other antiarrhythmic drugs, and in some cases had caused congestive heart failure or hypotension. Twelve patients were receiving digitalis, and in four the cause of the arrhythmia was thought to be digitalis excess. Fifteen patients were not receiving digitalis and their arrhythmia was presumed to have been related to recent cardiac infarction, open heart surgery, or other conditions.

The one failure in treating the ventricular arrhythmias was in a patient with a classical ventricular parasystole. On two attempts to abolish the arrhythmia, high plasma levels were obtained, the parasystolic firing rate slowed, but the focus was not abolished. Quinidine and xylcaine were also ineffective.

Eight of eight cases of ventricular tachycardia were successfully treated. These were
not included in table 1 since a complete set of samples for plasma levels was not obtained in any of these cases.

In eight cases we attempted without success to abolish ventricular premature contractions with injections of the amount of diluent that would contain 300 mg of DPH. All responded to subsequent injections of DPH.

Plasma DPH Concentration as a Function of Dose

In the patients of group I who received 50 or 100 mg of DPH every 5 min, the plasma level steadily rose. Figure 1 illustrates this for 10 cases which were selected to include the widest spread of data on plasma level as a function of cumulative dosage. The gradual rise in plasma level should be noted. Figure 1 demonstrates that a desired plasma level can be achieved in a steadily graded manner when DPH is administered every 5 min. It was rare for plasma level to increase more than 3 to 4 μg/ml after any dose. This predictably slow increase in level resulting from incremental administration allowed us to establish the minimal effective plasma levels for arrhythmias which were abolished by DPH.

Figure 2 demonstrates the plasma level of DPH at which ectopic ventricular rhythms were abolished in 24 of the patients of group I. Seventy per cent of the arrhythmias were abolished with plasma levels in the range of 10 to 18 μg/ml, although one arrhythmia did not respond until the plasma level reached 24 μg/ml.

As previously indicated, when ventricular premature contractions were abolished, further injections of DPH were withheld. In the majority of cases the arrhythmia recurred within 10 to 40 min. Administration of DPH was then resumed. Figure 3 shows the relationship of plasma DPH level to the presence of ventricular ectopic beats in a patient who had suffered recent myocardial infarction and was not receiving digitalis. Before administration of DPH there were 40 ventricu-
DIPHENYLHYDANTOIN PLASMA LEVELS

Figure 2

Plasma levels at which ventricular arrhythmias were abolished. Plasma DPH concentrations are plotted on the abscissa. The number of patients whose arrhythmia was abolished in each range of plasma level is represented on the ordinate as unfilled bars. The one patient whose arrhythmia was unaffected by DPH is represented by the filled bar; this unresponsive arrhythmia was a typical ventricular parasystole. Seventy per cent of the conversions occurred at plasma concentrations between 10 and 18 μg/ml. Only one patient required a plasma concentration above 18 μg/ml before conversion occurred.

Figure 3

The relationship between plasma DPH concentration (upper ordinate) and the presence of ventricular ectopic beats (lower ordinate) in a typical case from group I. Downward arrows represent doses of diphenylhydantoin. The abscissa between the upper and lower bars represents time in a nonlinear fashion; the time between the first and second arrows was 10 min, between the second and third arrows, 30 min, and between the third and fourth arrows, 75 min. When the plasma level exceeded 9.8 μg/ml, ventricular ectopic activity was absent. When the plasma level was below 9.5 μg/ml, ventricular ectopic activity was present. It can be seen that the supplementary doses of DPH needed to maintain the plasma level above the critical range were required with decreasing frequency.

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lar premature contractions per minute in a stable bigeminal pattern. One hundred milligram doses of DPH were repeated every 5 min until at a level of 10 μg/ml there were no ectopic beats. Administration of DPH was interrupted and over a period of 10 min the plasma level declined to 8 μg/ml. At this time the ventricular ectopic beats recurred. One dose of DPH then raised the plasma concentration to 11 μg/ml and ectopic activity ceased. Thirty minutes later the plasma level fell to 9.5 μg/ml and ectopic activity again recurred. When this sequence of events was repeated again, it became apparent that as long as a plasma concentration of about 9.5 μg/ml was maintained, ventricular ectopic activity was absent.

In this case, a definite relationship was established between plasma level and antiarrhythmic effect. In eight other patients a similar critical level was established.

When an effective plasma level has been produced by the incremental dosage method, supplementary doses need be given less and less frequently to maintain a given effective level. For instance, in figure 3, the time between events represented by downward bars one and two is 10 min and the time between downward bars three and four, 75 min.

Response of the Patients in Group II

DPH given intravenously for treatment of cardiac arrhythmias has been employed in previous studies, in doses of 100 to 500 mg administered within a few minutes. A commonly used dose has been 250 mg, the amount supplied in a single vial. For our study we injected 300 mg intravenously during a 1- to 3-min period. The decline in plasma level after this dose is shown for six typical patients in figure 4. There is a rapid decline to levels of 4 to 8 μg/ml, 20 to 40 min after injection. Very few responsive arrhythmias would be expected to respond at these plasma levels (fig. 2). Arrhythmias abolished by this method of administration often recurred after 10 to 20 min.

The decrease in plasma DPH concentration in figure 4 was not exponential; after larger
Before treatment there was steady bigeminy with occasional bursts of repetitive ventricular firing. Twelve hours after a 1,000-mg loading dose of DPH, the plasma level was 12.5 μg/ml and the number of ectopic beats had decreased. Note that the plasma level stabilized near 14 μg/ml and ventricular premature contractions were controlled until administration of the drug was discontinued. On the thirty-first day rare ectopic beats were noted; the ectopic ventricular beats disappeared without treatment after another week.

This case indicates the feasibility of oral treatment of arrhythmias which do not require immediate conversion. On several occasions we noted that attempts to begin maintenance doses on the third day caused the plasma level to fall and the arrhythmia to recur. Subsequently we always used a larger (500 mg) dose on the third day of treatment.

Response of the Patients in Group III

On a regimen of 400 mg/day, the peak plasma concentration of 10 to 12 μg/ml was reached only after 6 to 12 days. Thus, this was an unsatisfactory method for treating urgent cardiac arrhythmias because of the long period before a response was obtained.

Of the several oral methods employed, the most satisfactory was a loading dose of 1,000 mg given on the first day, doses of 500 to 600 mg on the second and third days, and then maintenance doses of 400 to 500 mg/day. This usually provided adequate control of responsive arrhythmias within 24 hr. Figure 5 presents data relevant to this point obtained from a patient who developed frequent ventricular premature contractions following myocardial infarction.

This patient was not receiving digitalis.

single intravenous doses, the fall in plasma level from 1 to 18 hr after injection is roughly exponential. Reasons for the nonexponential decline after smaller doses of DPH will be discussed later.

Figure 4

The decline in plasma DPH concentration with time after a single intravenous dose of 300 mg. Curves are shown from six patients in group II. The initial plasma levels were high when DPH was administered by this method, but the concentration rapidly fell. After 20 min, the plasma level ranged from 5 to 11 μg/ml. It may be noted by referring to figure 2 that the levels at 20 to 40 min are unlikely to produce an antarrhythmic effect.

Figure 5

Relationship between the plasma DPH concentration and frequency of ventricular premature contractions (VPC), in a patient from group III. The upper left ordinate represents relative frequency of ventricular ectopic beats; the lower left ordinate, the dosage of DPH in mg/day, and the right ordinate, the plasma level of DPH. By the second day of oral therapy, after 1,000 mg had been given, plasma levels were 14 μg/ml and VPCs were infrequent. When the oral dose was decreased on the third day, the plasma level of DPH fell to 12 μg/ml and VPCs recurred. The VPCs were abolished by a single, 100-mg intravenous dose (arrow) which raised the plasma level to 17.5 μg/ml and raised the total dose for the third day to 500 mg. No further ventricular ectopic activity was present on the maintenance dose of 400 mg/day. Note the return of VPCs on the thirtieth day after DPH had been discontinued and the plasma level had fallen below 6 μg/ml.
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Figure 6

Effect of DPH on heart rate, P-R interval, QRS duration, and the Q-T interval. The values representing measurements from a particular patient before and after DPH are connected by a line. The mean values of measurements are indicated by horizontal bars. The changes in heart rate (D. F. 17, t = 0.66, P < 0.05) and QRS duration (D. F. 9, t = 1.55, P < 0.05) were not significant. Changes in P-R interval were significant (D. F. 14, t = 2.75, P < 0.02). The Q-T interval, normalized for heart rate, shows an impressive decrease after DPH administration (D. F. 18, t = 5.07, P < 0.001).

Effects of Diphenylhydantoin
On the Electrocardiogram

Electrocardiograms obtained from an oscilloscopic recorder using rapid paper speeds were analyzed with regard to sinoatrial rate, P-R interval, QRS duration, and rate corrected Q-T interval, and for changes in the S-T segment and T-wave morphology. Measurement of intervals was made from recordings. Figure 6 shows the observed changes in heart rate and the measured intervals caused by DPH. No consistent direction of change was noted among the individual observations and no significant change in the mean heart rate was noted for the group. The mean changes in QRS and P-R intervals tended to decrease and in the case of the former were not significant. The change in P-R interval was significant (P < 0.02). Of great interest is the decrease in duration of the Q-T interval noted in the majority of cases and the significant decrease in the mean Q-T interval for the group after administration of the drug.

On Blood Pressure

Frequent measurements of arterial pressure were made during DPH administration. Most measurements were made with sphygmomanometer; in 10 patients continuous oscilloscopic monitoring of arterial pressure was obtained from a brachial arterial cannula.

In the patients of group III (oral doses), there was no significant change in blood pressure during therapy. In patients of group I (100-mg intravenous doses of DPH every 5 min), little change in blood pressure was noted until the accumulated dose approached 500 mg. At and above this level there was a mild decrease in systolic blood pressure (10 to 30 mm Hg). In patients of group II (single intravenous dose of 300 mg), the hypotensive effects were more marked. Systolic blood pressure usually decreased 20 to 45 mm Hg. If the arrhythmia being treated was the cause of systemic arterial hypotension, the blood pressure rose after the arrhythmia was abolished with DPH.

Undesirable Effects

The majority of the patients treated in this series received DPH for a relatively short time. Undesirable central nervous system effects were noted in 14 cases. Prominent symptoms were drowsiness, nystagmus, vertigo, and nausea, but rarely vomiting. When
these occurred, the plasma level was always above 20 µg/ml, although all patients with plasma levels exceeding 20 µg/ml did not have these symptoms. These plasma levels and the associated symptoms resulted from use of large doses in attempts to convert arrhythmias unresponsive to the drug. Symptoms abated as the plasma concentration fell. As plasma level determinations were not available until some time after the treatment of the arrhythmia, these symptoms often proved a useful guide to the use of this agent. If the arrhythmia was still present with the onset of these symptoms, we were aware that we had achieved a plasma level at which almost all responsive arrhythmias would convert and that persistence in the use of this agent was unlikely to be useful.

Two episodes, encountered during intravenous use of DPH, were initially thought to be untoward cardiovascular effects of the drug. The first was an episode of marked sinus slowing, profound hypotension, nausea, and diaphoresis after 400 mg of DPH had been given intravenously in 100-mg increments. Just prior to these events the patient complained of pain at the site of an arterial needle. The heart was paced and the symptoms subsided. Subsequently the plasma levels were noted to have risen only to a peak level of 10.5 µg/ml. Twelve hours after this episode the patient was given a larger dose, 500 mg, over a much shorter period without showing any of these effects. In retrospect, it would seem most reasonable to consider this sequence of events to represent a "vagovagal" episode secondary to pain at the site of the arterial needle. Had the patient not received the drug a second time, we would have attributed this episode to drug administration.

The second complication was cardiac arrest in an acutely ill patient with atherosclerotic heart disease, atherosclerotic cerebral vascular disease, severe peripheral vascular disease, and diabetes mellitus. The arrhythmia being treated was frequent ventricular premature contraction in the presence of second degree atrioventricular block with Wenckebach periods. Following seven 100-mg doses of DPH, the ventricular ectopic activity was abolished, the atrial rate increased, the blood pressure fell slightly, and a period of complete atrioventricular block ensued. There was a short delay before an idioventricular escape rhythm emerged at a rate of 46/min. Thirty minutes after this episode, the electrocardiogram became similar to those recorded prior to DPH administration except that ventricular ectopic activity was absent. The peak plasma level achieved during the study was 22 µg/ml.

Because of the extremely unstable circumstances under which the drug was given, we were not able to decide whether or not these events were caused by administration of the drug. Subsequent to this occurrence we studied several patients with second degree A-V block after a catheter pacemaker was placed in the right ventricle. Several of these patients were given up to 1,000 mg of DPH in the incremental manner without any increase in A-V block. However, it is clear that careful monitoring of the arterial pressure and the electrocardiogram is necessary during intravenous administration and that incremental doses should be used. Although we have no good evidence that DPH enhances A-V block, nevertheless when high-grade A-V block is present, we think it desirable to place a catheter pacemaker in the right ventricle before treating an arrhythmia with this or any other antiarrhythmic drug.

Discussion

Time Course of Plasma Level Decline and Routes of Administration

The fate and time course of intravenously administered DPH has been previously studied.17–19 Svensmark and associates17 observed the behavior of plasma concentrations of DPH after cessation of intravenous administration (9 to 11 mg/kg of body weight) for a period of 3 to 6 days. They found that, under those circumstances, the plasma concentration fell in a roughly exponential manner at a rate of 10 to 15%/hr. This rate of fall was definitely faster than the rate of fall (35 to 55%/24 hr) from similar plasma levels when the drug was
withdrawn from patients who had been on long-term oral doses.

Dill and associates estimated tissue and plasma concentrations of DPH 2 and 24 hr after single large doses given to rats. They noted that many tissues, especially liver and fat, had concentrations in great excess of plasma and that there were wide variations between various tissues. Such concentration gradients must be established before plasma levels can become stable. Once the various tissues come into equilibrium with the plasma concentration, withdrawal of the drug is accompanied by a fall in the plasma level which is dependent, in large part, on the metabolism of the drug which takes place in the liver.

In our studies the fall from peak plasma level after a single 300-mg dose was more rapid than that seen with larger single intravenous doses; the fall was not exponential. It seems reasonable to suggest that this rapid fall in plasma DPH concentration was due not only to metabolism of the drug by the liver, but also to its continued uptake into tissues having a higher affinity for the drug than plasma.

Not only did we find divided intravenous doses of 100 mg every 5 min a safer way of achieving a given plasma level than single large doses, but the plasma levels, thus attained, declined at a slower rate.

Oral doses of DPH are nearly completely absorbed from the gastrointestinal tract. Maximal plasma levels from a single oral dose are seen about 12 hr after ingestion. With continued administration of a constant daily oral dose, the plasma DPH concentration increases at a steadily decreasing rate. Doses of 3 to 6 mg/kg of body weight take 6 or 7 days to reach the peak plasma level. Larger doses (10 mg/kg of body weight) take 10 to 12 days to reach maximum levels.

In order to reach antiarrhythmic plasma levels in group III without delay, we employed large oral doses during the first 3 days of therapy. We then tapered the dosage to maintenance levels, usually 400 mg/day. If desired, the arrhythmia can be rapidly abolished by giving the drug intravenously initially, then giving the remainder of the first day's dose of 1,000 mg orally. If the arrhythmia recurs while the oral dose is being adjusted, it can readily be abolished by small intravenous doses of DPH without interrupting the oral schedule. This technique allows early effective treatment of arrhythmias and continuing control over a long period with minimal inconvenience to the patient and physician.

When DPH is used as the maintenance antiarrhythmic agent, one has to consider factors affecting the elimination of the drug. DPH is parahydroxylated in the liver and excreted as a glucuronic acid conjugate. Patients with severe hepatic disease may accumulate DPH in the plasma when on a prolonged, moderate dose. Phenobarbital is known to be an inducer of the hepatic microsomal enzyme which parahydroxylates DPH and accelerates the rate of its metabolism, thus decreasing its pharmacological effect. Drugs shown to decrease DPH metabolism, presumably by interfering with its parahydroxylation include bishydroxycoumarin, isonicotinic acid hydrazide together with paraaminosalicylic acid, and phenyramidol. Dose adjustments may be necessary when DPH is used in conjunction with these drugs. DPH can be used in patients with renal failure where quinidine therapy may be hazardous.

Effects of DPH on Arrhythmias in Relation to Plasma Level

Our data indicate that DPH is effective against ventricular arrhythmias which occur in a wide variety of situations, whether or not the patient has been receiving digitalis. With respect to atrial arrhythmias, DPH is moderately effective in paroxysmal atrial tachycardia, particularly that induced by digitalis excess. Attempts to convert atrial flutter and fibrillation to normal sinus rhythm were almost uniformly unsuccessful. We have had success in two cases of the rare entity of digitalis-induced atrial fibrillation; both reverted to normal sinus rhythm after administration of DPH (Goldreyer and Bigger,
unpublished observation). Thus, our clinical experience is in accord with that accumulated in animal experiments where this drug has been effective in controlling ventricular arrhythmias elicited by a wide variety of experimental techniques.

Several authors have stated that the drug has a short duration of action and is mainly useful in the acute treatment of arrhythmias.\textsuperscript{3, 4, 5, 7, 9, 27, 28} Our results indicate a definite relationship between the plasma level and the antiarrhythmic effect produced. The data show that 70% of the arrhythmias which responded to DPH did so at plasma levels between 10 and 18 \textmu g/ml; 90% responded at a plasma level below 18 \textmu g/ml. It was further shown that a critical effective plasma level could be demonstrated. When this critical plasma level was exceeded, by either oral or intravenous routes of administration, the antiarrhythmic effect was present. A smooth transition from the intravenous to the oral route of administration was usually possible without losing control of the arrhythmia being treated.

In our experience 100 mg of DPH administered intravenously every 5 min with observation of the electrocardiogram, blood pressure, and respiration is at least as safe as procaine amide and considerably safer than intravenously administered quinidine. It seems to have a wider margin of safety than these drugs when given by the oral route as well. Ingestion of very large doses of DPH has been reported\textsuperscript{29-31} with prolonged central nervous system symptoms and eventual survival of the patient. Prominent cardiac effects were not noted.

Using DPH intravenously in divided doses, we did not see severe hypotension or respiratory depression which may follow sudden large injections of this drug. The principal undesirable effects seen in our patients were central nervous system symptoms. Symptoms were encountered when plasma levels exceeded 20 \textmu g/ml and abated as plasma level fell below 20 \textmu g/ml; many patients do not find the central nervous system symptoms particularly unpleasant.

Actually, this correlation between plasma levels above 20 \textmu g/ml and central nervous system symptoms was a useful index of therapy. Ninety per cent of arrhythmias which respond to DPH did so at plasma levels below 18 \textmu g/ml; central nervous system symptoms usually indicate plasma levels exceeding 20 \textmu g/ml. Thus, an arrhythmia which has shown no sign of responding when these symptoms appear during administration of DPH, is unlikely to respond to further doses. Therefore, a rational decision to abandon DPH as an antiarrhythmic agent in such a case can be made without measurement of the plasma concentration.

There are many reasons for believing that the antiarrhythmic actions of diphenylhydantoin are quite different from those of quinidine and procaine amide. In the first place, DPH is ineffective in converting atrial flutter and fibrillation to normal sinus rhythm whereas quinidine was fairly effective in our cases when DPH failed. Both DPH and the quinidine-like drugs may be quite effective in abolishing ventricular arrhythmias having a variety of causes. However, DPH or quinidine is often effective against a particular arrhythmia when aggressive attempts with the other drug have been unsuccessful. DPH is effective in treating a variety of arrhythmias induced by digitalis excess without the unpredictable arrhythmias and conduction defects reported with the use of quinidine under these circumstances.

DPH and quinidine are clearly different in their electrocardiographic effects. The effect on heart rate tends to be minimal with DPH, whereas an increase in heart rate is not infrequently noted after administration of quinidine. These differences are more apparent when hypotension does not follow administration of either drug. In fact, slight decreases in heart rate may accompany moderate hypotension after administration of DPH, in patients with severe congestive heart failure.\textsuperscript{32} Neither DPH nor quinidine has marked effects on the P-R interval, although the P-R interval tends to shorten slightly after DPH. We have never seen the
QRS widen even after large doses of DPH; this is common after large doses of quinidine. Another marked difference between the two drugs is noted in the Q-T interval. Therapeutic doses of quinidine increase this interval; therapeutic doses of DPH significantly decrease the Q-T interval. This suggests that quinidine causes a prolongation of electrical systole and DPH, a shortening, which is in accord with laboratory studies.33

Thus, it would seem that DPH is an effective agent in treating ventricular arrhythmias having a wide variety of causes and in treating atrial tachycardia, especially if induced by digitalis excess. To be effective, DPH has to be maintained in an effective antiarrhythmic concentration in the plasma.

References


Relationship Between the Plasma Level of Diphenylhydantoin Sodium and Its Cardiac Antiarrhythmic Effects

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