Electrophysiologic Properties of Diphenylhydantoin

By Anthony R. Caracta, M.D., Anthony N. Damato, M.D., Mark E. Josephson, M.D., Michael A. Ricciutti, Ph.D., John J. Gallagher, M.D., and Sun H. Lau, M.D.

SUMMARY

The electrophysiologic properties of diphenylhydantoin (DPH) (5-10 mg/kg) intravenously was studied in 14 subjects using His bundle recordings and correlated with blood levels. Conduction through the A-V conducting system (AVCS) was studied at various paced atrial rates and refractory periods determined using programmed atrial premature depolarization within 10 min of drug administration. In 11 of 14 subjects the sinu atrial cycle length was shortened by an average of 110 msec, lengthened in three (average 116 msec). Conduction through the A-V node (AVN) was shortened in seven subjects (average 10 msec), lengthened in one (5 msec), and unchanged in the remaining six. Conducted by 5 msec. Prior to DPH, the longest refractory period of the AVCS was in the AVN in nine subjects, the atrium in four and the HPS in one. After DPH, the following effects were noted: (1) the effective refractory period (ERP) of the atria shortened in four subjects, lengthened in four, and was unchanged in the remaining six; (2) the ERP of the AVN shortened in 6/9 subjects, lengthened in 3/9; (3) functional refractory period of AVN shortened in six, prolonged in three subjects, and remained unchanged in five subjects; (4) the relative refractory period (RRP) of the HPS shortened in 7/7 subjects; (5) ERP of HPS in 1/1 subject shortened. Thus, DPH showed varied effects on A-V nodal conduction, inconsistent effect in the atrium, and consistent shortening of the refractory period of the HPS. The data suggest DPH differs from other antiarrhythmic drugs such as quinidine and procaine amide.

Additional Indexing Words:
Diphenylhydantoin
His-Purkinje system
A-V conduction
Refractory periods
Atroventricular node

DIPHENYLHYDANTOIN (DPH) has been used to treat a variety of cardiac arrhythmias occurring under different clinical situations.1-12 The results of a number of studies using isolated atrial muscle and Purkinje fiber preparations indicate that the electrophysiologic properties of DPH differ from those of other drugs such as procaine amide and quinidine.13-16,18 Some reports indicate that DPH enhances A-V nodal conduction time in the intact animal and human hearts11,12,17 while others noted a depression of A-V nodal conduction.9,20-22

The present study, involving 14 human subjects, was undertaken to determine what effects intravenously administered DPH has on refractoriness of the atrium, A-V node, and His-Purkinje system at paced cycle lengths. Measurements were also made of A-V nodal and His-Purkinje conduction time over a range of paced atrial rates. Correlation of the electrophysiologic effects with plasma levels were made.

Materials and Methods

Fourteen subjects underwent right heart catheterizations in the postabsorptive, nonsedated state. A signed consent was obtained for each patient. The presence or absence of heart disease was determined by clinical history, physical examination, chest X-ray, ECG, and cardiac catheterization when indicated. The essential clinical data are presented in table 1.

Under local anesthesia, a quadripolar electrode catheter was introduced percutaneously into the right antecubital vein and fluoroscopically positioned against the lateral wall of the high right atrium near its junction with the superior vena cava. The distal pair of electrodes was used to stimulate the atrium while the proximal pair was used to record a high right atrial electrogram. His bundle electrograms were obtained as previously described using a tripolar electrode catheter.27 Simultaneous recordings of standard electrocar-
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Table 1

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Drugs</th>
</tr>
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<tr>
<td>1</td>
<td>50</td>
<td>M</td>
<td>NHD</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>M</td>
<td>ASHD</td>
<td>Digoxin 0.25 mg OD</td>
</tr>
<tr>
<td>3</td>
<td>49</td>
<td>M</td>
<td>NHD</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>M</td>
<td>ASHD — old DMI</td>
<td>Digoxin 0.25 mg OD, Procaine amide 500 mg q 6 hours</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>M</td>
<td>ASHD</td>
<td>Nitroglycerin PNR</td>
</tr>
<tr>
<td>6</td>
<td>34</td>
<td>F</td>
<td>NHD</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>43</td>
<td>M</td>
<td>ASHD</td>
<td>Nitroglycerin PNR</td>
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<tr>
<td>8</td>
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<td>NHD</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>M</td>
<td>NHD</td>
<td>Digoxin 0.25 mg OD, Furosemide 40 mg OD</td>
</tr>
<tr>
<td>10</td>
<td>59</td>
<td>M</td>
<td>ASHD</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>62</td>
<td>M</td>
<td>ASHD — EH</td>
<td>Hydrochlorothiazide 50 mg OD</td>
</tr>
<tr>
<td>12</td>
<td>72</td>
<td>M</td>
<td>ASHD</td>
<td>Digoxin 0.25 mg OD</td>
</tr>
<tr>
<td>13</td>
<td>39</td>
<td>M</td>
<td>NHD</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>56</td>
<td>M</td>
<td>ASHD</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ASHD = arteriosclerotic heart disease; DMI = diaphragmatic wall myocardial infarction; EH = essential hypertension; NHD = no heart disease; OD = daily.

levels of DPH were determined using the technic of Dill et al.26 Statistical analysis of the data was performed by the Student t test for paired data.

Definition of Terms

A-H interval was used as an approximation of A-V nodal conduction time and was measured from the onset of the low atrial depolarization to the onset of the His deflection as recorded on the His bundle electrogram tracing. Normal values in our laboratory are 60–140 msec.

H-V interval was used to measure His-Purkinje conduction time and was measured from the onset of the His deflection to the earliest onset of ventricular depolarization. Normal values in our laboratory are 30–55 msec.

A1-H1 is the A-H interval of the basic rhythm.

A2-H2 is the A-H interval of the stimulated atrial premature depolarization (APD).

H1-H2 is the interval between the His bundle depolarizations of the basic and the premature beat.

Effective refractory period (ERP) of the atrium is defined as the longest S1-S2 interval at which S2 does not result in atrial depolarization.

Effective refractory period (ERP) of the A-V node is the longest A1-A2 interval at which A2 fails to conduct to the bundle of His.

Function refractory period (FRP) of the A-V node is the shortest interval between H1-H2 both of which are propagated from the atrium.

Effective refractory period (ERP) of the His-Purkinje system is the longest H1-H2 interval at which H2 fails to conduct to the ventricles.

Relative refractory period (RRP) of the His-Purkinje system is the longest H1-H2 at which H2 conducts to...
the ventricles with a longer H-V interval than that of
the basic drive beat or with a QRS with aberrant
configuration.

Results
The effects of DPH on sinus cycle length and A-V
conduction times are presented in table 2.
Sinus cycle length. DPH caused no clinically
significant changes in sinus rate \(P > 0.05\). In 11 of
14 subjects the sinus cycle length was shortened by
an average of 110 msec (range 30–230 msec). In
three subjects, sinus cycle length was increased by
an average of 116 msec (range 40–250 msec).

A-V nodal conduction time (A-H interval). In
seven subjects, the A-H interval during sinus
rhythm decreased by an average of 10 msec (range
5–20 msec) while in six subjects DPH caused no
change. In one subject, DPH increased A-H interval
by 5 msec. The average change of 4 msec
\(P < 0.05\) was clinically insignificant.

His-Purkinje conduction time (H-V interval).
Following DPH, the H-V interval was unchanged.

Table 3
Effects of Diphenylhydantoin on Refractory Period of the A-V Conducting System

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Faced cycle length (msec)</th>
<th>ERP of Atrium (msec)</th>
<th>ERP of AVN (msec)</th>
<th>ERP of HPS (msec)</th>
<th>RRP of HPS (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>1</td>
<td>800</td>
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<td>330</td>
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<td>260</td>
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<td>3</td>
<td>750</td>
<td>250</td>
<td>210</td>
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<td>4</td>
<td>700</td>
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<td>7</td>
<td>800</td>
<td>350</td>
<td>320</td>
<td>430</td>
<td>430</td>
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<tr>
<td>8</td>
<td>900</td>
<td>360</td>
<td>380</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
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<td>240</td>
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<tr>
<td>11</td>
<td>800</td>
<td>260</td>
<td>270</td>
<td>430</td>
<td>430</td>
</tr>
</tbody>
</table>

Mean 277±11 274±12 388±41 368±29 450±25 448±20 443±19 413±19

\(P value\) \(P > 0.4\) \(P > 0.2\) \(P > 0.2\) \(P < 0.005\)

*Electrophysiologic studies limited due to atrial refractoriness.
DIPHENYLHYDANTOIN

in all but two subjects (nos. 7 and 14) in whom it increased by 5 msec. These latter subjects had abnormal H-V intervals in the control situation. However, DPH did not prolong His-Purkinje conduction in six other subjects who also had H-V intervals which were abnormal in the control period. The average change of 1 msec was both clinically and statistically insignificant ($P > 0.1$).

Findings during atrial pacing. A-V nodal conduction time (A-H interval). During atrial pacing at

![Figure 1](http://circ.ahajournals.org/)

**Figure 1**

*Effect of DPH on the effective refractory period of the A-V node. (A and B) Leads I, II, III, V<sub>1</sub>, high right atrial electrogram (HRA), His bundle electrogram (HBE), and time lines at 10 and 100 msec. A shows atrial pacing at a cycle length of 700 msec ($A_{1}-A_{2}$ with an A-H of 140, H-V 40). An atrial premature depolarization ($A_{2}$) delivered at a coupling interval of 310 msec blocked within the A-V node. (B) After 500 mg of DPH at a blood level of 15.2 µg/ml. At the same cycle length ($A_{1}-A_{2}$ of 700 msec), the A-H is shortened by 25 msec. $A_{2}$ delivered at an $A_{1}-A_{2}$ coupling of 310 msec now is conducted with an A-H of 290, H-V remaining constant.*

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rates ranging between 90 and 160 beats/min A-V nodal conduction was enhanced in 10 subjects by an average of 23 msec following DPH. In the remaining four subjects A-V nodal conduction was delayed by an average of 18 msec.

His-Purkinje conduction time (H-V interval). The H-V interval remained constant at all paced atrial rates. In the two patients who had a 5-msec increase in H-V interval at sinus rhythm, no further increase occurred during atrial pacing.

The results of refractory period studies before and after DPH are listed in table 3.

Atrium. The effect of DPH on the effective refractory period of the atrium was variable. In four subjects, the effective refractory period was increased by an average of 12 msec, and in four the

Figure 2

Effect of DPH on the relative refractory period (RRP) of the His-Purkinje system. (A and B) ECG leads I, II, III, V1, HRA, HBE, and time lines at 10 and 100 msec. (A) Before DPH, the atrium is being paced at a cycle length of 750 msec (A1-A1), A1-H1 105 msec, H1-V1 35 msec. An A2 delivered at a coupling of 320 msec conducts with an aberrantly conducted beat with an A2-H2 of 160 msec, H2-V2 40 msec, and an H1-H2 of 380 msec. (B) After DPH (blood level 23.5 µg/ml), at the same cycle length, an A2 delivered at 320 msec conducts with an A2-H2 of 170 msec, H2-V2 35 msec but not aberration at the same H1-H2 interval.

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effective refractory period of the atria decreased by an average of 22 msec. Six subjects demonstrated no change following DPH. These changes were not clinically significant (P > 0.4).

A-V node: Effective refractory period. The effective refractory period of the A-V node could be determined in only nine patients. In the remaining five subjects, the effective refractory period of the atria was first encountered. In six subjects DPH shortened the effective refractory period of the A-V node by an average of 46 msec. Figure 1 is representative of these findings. In three subjects it was prolonged by 33 msec.

Functional refractory period. DPH had variable effects on the functional refractory period of the A-V node. In six patients the functional refractory period of the A-V node was shortened by an average of 36 msec and in three it was prolonged by an average of 23 msec. In the remaining five subjects there was no change.

His-Purkinje system: Relative refractory period. The relative refractory period of the His-Purkinje system was significantly shortened in 7/7 subjects. The average change was 30 msec (P < 0.005). Figure 2 depicts this finding.

Effective refractory period. The effective refractory period of the His-Purkinje system could only be determined in one subject. There was shortening of the effective refractory period by 10 msec.

Blood levels. Table 4 lists the individual blood level determinations. Eleven subjects did not develop any untoward effects due to the drug. Three subjects demonstrated a fall in systolic blood pressure of 10–20 mg Hg and also complained of pain at the site of injection.

**Table 4**

Diphenylhydantoin Blood Levels (μg/ml)

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Dose DPH (mg)</th>
<th>Control</th>
<th>Sample 1</th>
<th>Sample 2</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>650</td>
<td>0.8</td>
<td>15.5</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>500</td>
<td>0.0</td>
<td>11.6</td>
<td>10.4</td>
</tr>
<tr>
<td>3</td>
<td>500</td>
<td>0.0</td>
<td>10.3</td>
<td>8.2</td>
</tr>
<tr>
<td>4</td>
<td>500</td>
<td>0.1</td>
<td>34.0</td>
<td>14.0</td>
</tr>
<tr>
<td>5</td>
<td>500</td>
<td>0.5</td>
<td>23.5</td>
<td>18.7</td>
</tr>
<tr>
<td>6</td>
<td>500</td>
<td>0.5</td>
<td>15.2</td>
<td>9.8</td>
</tr>
<tr>
<td>7</td>
<td>500</td>
<td>0.0</td>
<td>15.6</td>
<td>13.2</td>
</tr>
<tr>
<td>8</td>
<td>250</td>
<td>2.9</td>
<td>21.9</td>
<td>16.3</td>
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<td>9</td>
<td>250</td>
<td>0.8</td>
<td>11.3</td>
<td>5.5</td>
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<td>2.9</td>
<td>12.6</td>
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<tr>
<td>11</td>
<td>250</td>
<td>0.5</td>
<td>29.4</td>
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<td>14</td>
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<tr>
<td>Average</td>
<td>418</td>
<td>0.6</td>
<td>18.1</td>
<td>12.4</td>
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</table>

**Discussion**

It has been well demonstrated in Purkinje fiber studies, that the electrophysiologic effects of DPH on transmembrane action potential recordings differ from those of other antiarrhythmic agents such as quinidine and procaine amide.2, 12, 13, 16, 19, 24 In the moderate doses, DPH shortens both action potential duration and effective refractory period; the latter to a lesser extent than the former. DPH shifts the membrane responsiveness curve to the left and in states of depressed conduction the drug shortens interelectrode conduction time. Unlike procaine amide and quinidine, DPH did not depress conduction within the His-Purkinje system.

The results of this clinical study are consistent with the results from isolated Purkinje fiber studies. DPH did not affect His-Purkinje conduction time (H-V interval) during sinus rhythm and over a wide range of paced atrial rates. Only two patients showed a minimal increase of 5 msec in the H-V interval. In contrast, therapeutic doses of procaine amide and quinidine almost invariably cause a prolongation of His-Purkinje time in man both at sinus and paced atrial rates.2, 25, 32 The effects of lidocaine on His-Purkinje conduction time are more like those of DPH. Clinical studies in man have demonstrated that both procaine amide and quinidine cause a prolongation of the relative refractory period of the His-Purkinje system while lidocaine shortens the relative refractory period. The shortening of the RRP of His-Purkinje system by DPH in all seven subjects was statistically significant (P < 0.005). DPH shortened, by a relatively small amount the effective refractory period of the His-Purkinje system in the one patient in whom this could be determined. This effect is similar to that produced by lidocaine.31 On the other hand, procaine amide and quinidine cause an increase in the effective refractory period of the His-Purkinje system.22 (Josephson ME, Batsford WP, Seides SF, Caracta AR, Lau SH, Damato AN: Unpublished data).

Diphenylhydantoin has been reported to both enhance and delay A-V nodal conduction time.9, 11, 12, 17, 20–22 In a previous report from this laboratory,12 DPH was found to consistently enhance A-V nodal conduction in man. The results of the present study are less consistent; however a majority of patients (10) demonstrated enhanced A-V nodal conduction following the drug while in four patients conduction was delayed. Consistent with these findings is the fact that in a majority of
patients (six of nine), DPH resulted in a shortening of the effective refractory period of the A-V node.

Microelectrode studies have demonstrated that the effects of DPH on the electrophysiologic properties of atrial tissue differ from those effects on Purkinje fibers. The variable effects of DPH on atrial refractoriness in this study are consistent with the clinical observation that this drug, for the most part, is ineffective in the treatment of most atrial arrhythmias.

The therapeutic blood level of DPH for the treatment of most ventricular arrhythmias is generally between 10 and 18 µg/ml. Effectiveness can also be seen at lower levels. In the present study, the effects of DPH on the electrophysiologic properties of the A-V conducting system were studied at blood levels known to be therapeutic for most ventricular arrhythmias.

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