Diphenylhydantoin Prevention of Arrhythmias in the Digitalis-Sensitized Dog after Direct-Current Cardioversion

By RICHARD H. HELFANT, M.D., BENJAMIN J. SCHERLAG, PH.D., and ANTHONY N. DAMATO, M.D.

SUMMARY

The ability of diphenylhydantoin to prevent arrhythmias induced by synchronized direct current shocks after digitalis sensitization was evaluated. In the control state, an average of 155 watt-seconds was required to produce ventricular tachycardia. Immediately after recovery from digitalis toxicity, an average of 23 watt-seconds produced ventricular tachycardia. The administration of diphenylhydantoin at this time immediately increased the threshold required for ventricular tachycardia to an average of 363 watt-seconds. In eight studies, diphenylhydantoin was given during cardioversion-induced ventricular tachycardia and converted all cases to regular sinus rhythm. These findings indicate that diphenylhydantoin may be of prophylactic value prior to direct current cardioversion in a digitalized patient. Conversely, diphenylhydantoin would also be useful in the management of ectopic beats that may occur in digitalized patients after cardioversion.

Additional Indexing Words:
Ectopic beats  Electrical energy threshold  Ventricular automaticity

DIRECT CURRENT cardioversion has become generally accepted as an effective method for treating ectopic cardiac arrhythmias. However, one of the major problems associated with its use is that patients taking digitalis may develop serious arrhythmias after the direct current shock.1-4 The prevention and treatment of the arrhythmias that develop after countershock is therefore of clinical importance.

Diphenylhydantoin has been found clinically to be an effective antiarrhythmic agent of particular value in treating arrhythmias resulting from digitalis excess.5-8 In this study, an evaluation was made of the ability of diphenylhydantoin to prevent direct-current shock induced arrhythmias after digitalis sensitization.

Methods

Sixteen adult mongrel dogs were anesthetized with intravenous sodium pentobarbital (30 mg/kg) after an overnight fast. Two electrode paddles, 9 cm in diameter, were covered with conductive jelly and manually placed and held on either side of the shaved chest at the level of the cardiac apex beat. Direct current discharges, synchronized to occur during the QRS complex, were repetitively applied at 30-second intervals. Beginning at 10 watt-seconds, the energy was progressively increased to 25, 50, 100, 200, 300, and 400 watt-seconds, until ventricular tachycardia, defined as four or more consecutive ventricular premature beats, was produced. The direct-current shock was repeated twice at each energy level before proceeding to the next highest level.

Ouabain was then administered (7.5 µg/kg injection, followed by 3.0 µg/kg/min infusion) until ventricular tachycardia was produced. As soon as regular sinus rhythm returned (after
DIPHENYLHYDANTOIN PREVENTION OF ARRHYTHMIAS

Table 1

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Control</th>
<th>After digitalis</th>
<th>After diphenylhydantoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>25</td>
<td>300</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>25</td>
<td>&gt;400</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
<td>25</td>
<td>&gt;400</td>
</tr>
<tr>
<td>4</td>
<td>400</td>
<td>50</td>
<td>&gt;400</td>
</tr>
<tr>
<td>5</td>
<td>200</td>
<td>25</td>
<td>&gt;400</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>25</td>
<td>300</td>
</tr>
<tr>
<td>7</td>
<td>200</td>
<td>25</td>
<td>&gt;400</td>
</tr>
<tr>
<td>8</td>
<td>200</td>
<td>10</td>
<td>400</td>
</tr>
<tr>
<td>9</td>
<td>100</td>
<td>10</td>
<td>200</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>10</td>
<td>&gt;400</td>
</tr>
<tr>
<td>11</td>
<td>100</td>
<td>10</td>
<td>&gt;400</td>
</tr>
<tr>
<td>12</td>
<td>200</td>
<td>50</td>
<td>&gt;400</td>
</tr>
<tr>
<td>13</td>
<td>100</td>
<td>10</td>
<td>300</td>
</tr>
<tr>
<td>14</td>
<td>200</td>
<td>10</td>
<td>300</td>
</tr>
<tr>
<td>15</td>
<td>50</td>
<td>25</td>
<td>400</td>
</tr>
<tr>
<td>16</td>
<td>200</td>
<td>25</td>
<td>&gt;400</td>
</tr>
<tr>
<td>Av:</td>
<td>155</td>
<td>23</td>
<td>363</td>
</tr>
<tr>
<td>S.D.</td>
<td>70</td>
<td>12</td>
<td>80</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

10 to 30 minutes), the electrical energy level required to produce ventricular tachycardia was again determined by the procedure described. At this time (within 30 seconds), diphenylhydantoin (5 mg/kg) was administered intravenously, and the electrical energy threshold necessary to cause ventricular tachycardia was again ascertained.

Results

The results of this study are summarized in table 1. In the undigitalized state, an average of 155 watt-seconds was required to produce ventricular tachycardia. A direct current shock at any given energy level did not affect the threshold for ventricular tachycardia since the second applied shock never produced ventricular tachycardia when the initial shock at the same energy level failed to do so. This confirms the finding of others that repeated direct current shocks do not affect the threshold for ventricular tachycardia.

After recovery from digitalis toxicity, an average of 23 watt-seconds produced ventricular tachycardia. The administration of diphenylhydantoin at this time immediately increased the threshold required to produce ventricular tachycardia to an average of 363 watt-seconds; in 9 of the 16 studies, ventricular tachycardia was not produced at levels of 400 watt-seconds, the upper limit of electrical energy available for testing (fig. 1). The lowest level was 200 watt-seconds, which was seen in one study.

In eight studies, diphenylhydantoin was administered during the sustained ventricular tachycardia produced by direct-current shock after digitalis sensitization. In all these cases, the ventricular arrhythmia was converted to regular sinus rhythm, and the electrical energy to produce ventricular tachycardia was immediately elevated to an average of 350 watt-seconds. An example is seen in figure 2.

Discussion

Several reports have indicated that patients receiving digitalis are prone to develop serious ventricular arrhythmias following cardversion. It has been shown experimentally that the threshold necessary to produce ventricular arrhythmias with direct-current shock is markedly decreased following recovery from digitalis toxicity. The results of the present study confirm this finding in that the electrical energy threshold necessary to produce ventricular tachycardia decreased from an average of 155 to 23 watt-seconds.

The effectiveness of diphenylhydantoin as an antiarrhythmic agent has been established, and it appears that this agent has particular clinical value in the treatment of digitalis-induced arrhythmias. In this respect, diphenylhydantoin may be superior to agents such as procaine amide, since diphenylhydantoin decreases ventricular automaticity, negligibly affects intraventricular conduction, and enhances atrioventricular conduction.

It has been shown experimentally that when diphenylhydantoin is given prophylactically, the dose of digitalis necessary to produce toxicity is markedly increased. This indicates that diphenylhydantoin can inhibit the sensitization of the heart to the electrophysiological manifestations of digitalis excess. In the present study, the administration of diphenylhydantoin (in doses

Circulation, Volume XXXVII, March 1968
considered comparable to those used clinically) immediately after recovery from digitalis-induced arrhythmias increased the electrical energy threshold necessary to produce ventricular tachycardia from an average of 27 to 360 watt-seconds. This indicates that diphenylhydantoin effectively protects against the development of cardioversion-induced arrhythmias in the digitalis sensitized heart.

In addition, in eight studies, diphenylhydantoin was given during the ventricular tachycardia produced by cardioversion after digitalis sensitization and reverted all of these cases to regular sinus rhythm. The temporal relationships in these eight studies indicated that the effects of digitalis were still present at the time of diphenylhydantoin administration. It has previously been shown that ouabain sensitizes the heart to direct-current countershock for more than 30 minutes.9 In the present study, diphenylhydantoin was administered 30 seconds after the electrical energy level in the digitalis-sensitized state was determined. The direct-current shocks were then repeated within 30 seconds. Direct-current shocks applied at this time in the

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

**Figure 1**

A representative experiment demonstrating the electrical energy level of direct-current countershock necessary to produce ventricular tachycardia during control, after recovery from digitalis toxicity and after diphenylhydantoin. In the control panel, 150 watt-seconds (WS) direct-current countershock induces a short run of ventricular tachycardia which returns to regular sinus rhythm. In the second panel, after digitalis-induced ventricular tachycardia returned to regular sinus rhythm, 25 WS direct-current countershock produces a more prolonged ventricular tachycardia. In the third panel, immediately after regular sinus rhythm reappears, diphenylhydantoin treatment effectively protects from the development of ventricular tachycardia at an energy level of 400 WS.
absence of diphenylhydantoin administration invariably resulted in ventricular tachycardia at the same energy level as immediately after recovery from digitalis toxicity. Therefore, the effects of digitalis were still present when the actions of diphenylhydantoin were studied.

The results of this study may have important clinical implications. When elective cardioversion is indicated, it has been recommended that digitalis be withheld for one\(^4\) or more\(^3\) days before the procedure. If the clinical situation militates against this, or in emergency situations in which cardioversion...
becomes necessary in a digitalized patient, the administration of prophylactic diphenylhydantoin prior to the direct-current shock may be of value. Conversely, diphenylhydantoin would also be useful in the management of ectopic beats that may occur after cardioversion in a digitalized patient. The latter use of diphenylhydantoin has been described clinically.4, 13

Acknowledgment

The authors wish to thank Misses Joan Cumming, Audrey Pederson, and Loretta Carey, for their technical assistance, and Mrs. Anne Mazzella, for her aid in the preparation of the manuscript.

References

Diphenylhydantoin Prevention of Arrhythmias in the Digitalis-Sensitized Dog after Direct-Current Cardioversion

RICHARD H. HELFANT, BENJAMIN J. SCHERLAG and ANTHONY N. DAMATO

Circulation. 1968;37:424-428
doi: 10.1161/01.CIR.37.3.424
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1968 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/37/3/424

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/