Influence of Diphenylhydantoin on Electrophysiological Properties of the Canine Heart

By Robert A. Rosati, M.D., James A. Alexander, M.D., Stephen F. School, M.D., and Andrew G. Wallace, M.D.

ABSTRACT

These studies were designed to examine the electrophysiological effects of diphenylhydantoin (Dilantin) on the heart of awake dogs. Recording electrodes were implanted over the sinoatrial node, bundle of His, and right bundle branch, and studies were performed 2 to 6 weeks following recovery. Diphenylhydantoin (10 mg/kg) increased heart rate, shortened A-V conduction time and had little or no effect on conduction velocity in Purkinje tissue or total ventricular activation time. Similar effects were noted when heart rate was controlled by pacing. Following cardiac denervation, diphenylhydantoin decreased heart rate and prolonged A-V conduction time. It raised the threshold of atrial and ventricular muscle with no change of refractory periods. In dogs with heart block, it decreased the maximal rate at which the atria would respond to stimulation. When ventricular tachycardia was induced in dogs with heart block, by toxic doses of deslanoside, diphenylhydantoin abolished the ectopic tachycardia and restored the control rhythm.

ADDITIONAL KEY WORDS antiarrhythmic drugs heart block sympathetic nervous system digitalis

In 1950, Harris and Kokernot (1) first suggested that diphenylhydantoin might be useful in the management of cardiac arrhythmias. They demonstrated that large doses rapidly converted ventricular tachycardia to normal rhythm after experimental myocardial infarction in dogs. It was reported subsequently that diphenylhydantoin also was effective in the treatment of ventricular arrhythmias in dogs with ouabain intoxication (2) and of arrhythmias produced by the application of aconitine to the wall of the atrium (3). During recent years, diphenylhydantoin has been used to treat certain patients with disturbances of cardiac rhythm. It has been especially useful in the management of arrhythmias produced by digitalis overdose (4-6) and those that follow open heart surgery (7). Despite the reports noted above, its effects on the heart are still poorly understood. These studies were designed to examine the electrophysiologic effects of diphenylhydantoin and to define more clearly some of the mechanisms that might be responsible for its therapeutic action in disturbances of cardiac rhythm.

Methods

Experiments were performed on three groups of dogs. The first group consisted of 5 dogs; they were anesthetized, and recording electrodes were implanted on the bundle of His and the right bundle branch during separate periods of temporary occlusion of the venae cavae. A similar recording electrode also was implanted over the region of the sinoatrial node; pacing electrodes were sutured to the epicardial surface of the right atrium and the right ventricle. The animals were allowed to recover from the surgical procedure and were studied 2 to 6 weeks later in the awake state. During this interval the dogs were trained to sit quietly, and they became accustomed to the laboratory.
Signals from each of the recording electrodes were amplified with Tektronix 122 preamplifiers, displayed on a Tektronix 561-A oscilloscope, and recorded on a Hewlett-Packard 3917-A tape recorder. Frequencies below 80 cycle/sec and above 1,000 cycle/sec were filtered to sharpen the desired signals. A lead II electrocardiogram also was recorded. After each study, representative segments were selected from tape and reproduced on a Brush photographic oscillograph at a paper speed of 10 inches/sec. From these recordings, sinus rate, conduction time across the A-V node, conduction time in the Purkinje system, and total ventricular activation time were measured. Intervals could be measured reproducibly to the nearest 1 msec. Excitability threshold was estimated by the amount of current required to produce a propagated response well after the refractory period of a basic beat. The effective refractory period was defined as the shortest interval after a basic beat at which a pulse of twice threshold produced a propagated response.

The following protocol was observed during each experiment. The excitability and effective refractory period of atrial and ventricular muscle were determined at a heart rate of 188 beats/min. Electrograms were then recorded at the animal's spontaneous heart rate and at paced rates from 150 to 240 beats/min. Each animal was then given 10 mg/kg of diphenylhydantoin intravenously over a period of 5 min; 1 mg/kg per hr was then infused throughout the remainder of the experiment. The initial dose of 10 mg/kg was selected because preliminary studies showed that it produced a plasma concentration of diphenylhydantoin of 8 to 10 mg/liter. The infusion rate was based on the observation that after an intravenous injection the plasma concentration decreased approximately 10%/hr (8). Approximately 45 min after the initial dose, excitability and refractoriness were again estimated, and electrograms were recorded at the animal's spontaneous heart rate and at paced rates of 150 to 240 beats/min. Similar studies were performed in 3 dogs 4 to 6 weeks after total extrinsic denervation of the heart (9). The catecholamine concentration in ventricular muscle, determined when the dogs were killed, was less than 0.03 μg/g of muscle in denervated preparations.

In a second group, consisting of 6 dogs, chronic A-V block was produced by tightening a ligature around the bundle of His. Recording electrodes were implanted on the right and left atria and on the right ventricle, and a stimulating electrode was implanted on the right atrial appendage. The dogs were allowed to recover for 1 to 2 weeks before they were studied. With each dog resting quietly in the awake state, right and left atrial electrograms were monitored. The maximal rate at which the atria would respond to regular stimuli was determined by pacing the right atrium stepwise from 150 to 450 beats/min. The rate at which either the right or the left atrial electrogram no longer followed the pacing stimulus in a 1:1 relation was observed before and 10 to 20 min after diphenylhydantoin was given. Recordings of the electrocardiogram and a ventricular electrogram also provided evidence regarding the effects of diphenylhydantoin on spontaneous ventricular rate in awake dogs with heart block.

The effect of diphenylhydantoin on digitalis-facilitated pacemaker activity was observed in 3 of the 6 dogs with heart block. These dogs were anesthetized lightly with thiamyl sodium and ventilated with a Harvard respirator. Deslanoside (0.3 mg/kg) was administered intrave-

### Table 1

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Heart rate (beats/min)</th>
<th>A-H (msec)</th>
<th>H-P (msec)</th>
<th>H-S (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>138 Before 151 After</td>
<td>62 Before 58 After</td>
<td>18 Before 18 After</td>
<td>65 Before 64 After</td>
</tr>
<tr>
<td>2</td>
<td>139 Before 168 After</td>
<td>51 Before 35 After</td>
<td>23 Before 23 After</td>
<td>82 Before 87 After</td>
</tr>
<tr>
<td>3</td>
<td>72 Before 88 After</td>
<td>49 Before 58 After</td>
<td>14 Before 15 After</td>
<td>60 Before 62 After</td>
</tr>
<tr>
<td>4</td>
<td>128 Before 176 After</td>
<td>82 Before 67 After</td>
<td>11 Before 12 After</td>
<td>62 Before 63 After</td>
</tr>
<tr>
<td>5</td>
<td>100 Before 125 After</td>
<td>63 Before 61 After</td>
<td>10 Before 10 After</td>
<td>58 Before 61 After</td>
</tr>
</tbody>
</table>

Change* +27 ± 6 -6 ± 5 +0.4 ± 0.3 +2 ± 1

A-H = interval from atrial septum to bundle of His; H-P = interval from bundle of His to Purkinje spike; H-S = interval from bundle of His to ventricular septum.

*Mean and SE of the changes.

Dilantin, Parke-Davis & Company.

Surital, Parke-Davis & Company.

Cedilanid, Sandoz Pharmaceuticals.
nously while a lead II electrocardiogram was monitored. After ventricular arrhythmias, such as ventricular tachycardia, appeared, 10 mg/kg diphenylhydantoin was administered intravenously, and electrocardiographic monitoring was continued for 30 to 45 min.

In a third group, consisting of 5 dogs, ventricular fibrillation threshold was determined before and after diphenylhydantoin. These studies were performed in anesthetized animals with open chests. Fibrillation threshold was determined using a square-wave shock during the vulnerable period (10). The determinations were made before and 30 min after 10 mg/kg diphenylhydantoin was given.

Results

Data illustrating the effects of diphenylhydantoin on sinus rate and conduction intervals in 5 normal dogs are presented in Table 1. Sinus rate increased in all 5 and A-V conduction time (A-H interval) decreased in 4. Conduction time in specialized Purkinje tissue (H-P interval) increased in only 2 of the dogs and total ventricular activation time, (H-S interval) increased slightly in 4. Representative records from 1 of the dogs are shown in Figure 1.

Data from 4 dogs whose hearts were paced from the atrium at a rate of 188 beats/min before and after receiving diphenylhydantoin are presented in Table 2. In Figure 2 tracings from 1 dog illustrate the effects during atrial pacing.

Table 2

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Heart rate (beats/min)</th>
<th>A-H (msec)</th>
<th>H-P (msec)</th>
<th>H-S (msec)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
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<tr>
<td>1</td>
<td>188</td>
<td>71</td>
<td>18</td>
<td>19</td>
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<td>101</td>
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<td>13</td>
</tr>
<tr>
<td>4</td>
<td>188</td>
<td>115</td>
<td>10</td>
<td>11</td>
</tr>
</tbody>
</table>

Change* | -17 ± 6 | +1 ± 0.3 | +4 ± 0.6 |

Abbreviations are the same as in Table 1.

*Mean and se of the changes.
Effects of diphenylhydantoin on conduction in a normal awake dog. The heart was paced from the right atrium at 188 beats/min. Abbreviations are the same as in Figure 1.

Effects of diphenylhydantoin on conduction in an awake dog with a totally denervated heart. The heart was paced from the right atrium at 188 beats/min. Abbreviations are the same as in Figure 1.

Data from 1 dog with implanted electrodes were not included in Tables 1 and 2 because of the presence of an arrhythmia. Before being given diphenylhydantoin, this dog manifested the Wenckebach phenomenon and varying degrees of A-V block at paced rates from 120 to 240 beats/min. After diphenylhydantoin was given, normal rhythm and conduction were restored and the dog's heart could be paced up to a rate of 150 beats/min without A-V block.

To provide some insight into the possible contribution of autonomic factors to the responses observed in normal dogs, diphenylhydantoin was given to 3 dogs with chronically denervated hearts. In contrast to normal animals, the sinus rate decreased, and A-V conduction time was prolonged at spontaneous and paced rates. The effects of diphenylhydantoin in 1 of the dogs with a denervated heart are shown in Figure 3.

The effects of diphenylhydantoin on excitability and refractoriness of atrial and ventricular muscle were examined in each dog.

Circulation Research, Vol. XXI, November 1967
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During control observations, the average atrial threshold was 1.1 mA. Atrial threshold increased in all of the dogs after they were given diphenylhydantoin. The average change was an increase of 0.6 mA (P < .05). Ventricular threshold during control periods averaged 0.4 mA and increased in 4 of the 5 dogs after diphenylhydantoin. The average change was an increase of 0.2 mA (P < .05). Diphenylhydantoin produced small and inconsistent changes in the effective refractory period of atrial and ventricular muscle. Data from 1 dog illustrating the effects of diphenylhydantoin on excitability and refractoriness of atrial and ventricular muscle are shown in Figure 4.

The effect of diphenylhydantoin on the maximal rate at which the atria would respond regularly to stimulation was measured in 6 dogs with chronic heart block. Before diphenylhydantoin was given, the atria responded to each stimulus up to rates of 400-450 beats/min (average 438/min). After it was given, the maximal response rate decreased in each dog. After 5 mg/kg, the average decrease was 16%, and after 10 mg/kg, 26%.

The effects of diphenylhydantoin on ventricular pacemaker activity were examined in 4 awake dogs with chronic heart block. There was either no change or only a transient increase of the spontaneous ventricular rate. Three of these dogs were given deslanoside until ventricular tachycardia was produced. In 2 of the 3, 10 mg/kg diphenylhydantoin slowed the ventricular rate, but an additional 5 mg/kg was required to abolish the arrhythmia and to restore control rhythm. The effect on the third dog is shown in Figure 5. Following deslanoside, there was a bigeminal type of ventricular tachycardia. Within 1 min after the intravenous administration of 10 mg/kg diphenylhydantoin, cardiac arrest occurred, followed by a restoration of the
Control

VR = 55

Deslanoside (l.6mg) 50 min

VR = 62

60 min

VR = 150

DPH (l0mg/kg)

Arrest

1 min after DPH

VR = 65

FIGURE 5

Effects of diphenylhydantoin on ventricular tachycardia induced by digitalis in a dog with heart block. Fifty minutes after the administration of 0.16 mg/kg deslanoside to a 10-kg dog heart rate increased to 62 beats/min; by 60 min, a bigeminal type of ventricular tachycardia had developed. The two bottom panels are a continuous tracing showing the response to diphenylhydantoin (DPH). See text for further details.

Discussion

The mechanism of action of diphenylhydantoin in the treatment of convulsive disorders (11-14) and in trigeminal neuralgia is thought to be related to its ability to raise membrane threshold to excitation and to prevent the hyperexcitability produced by repetitive stimulation, hypotremia, or hypocalcemia (15). Diphenylhydantoin also decreases the intracellular concentration of sodium in brain cells and skeletal and cardiac muscle (16). Although little is known about the antiarrhythmic effects of diphenylhydantoin on the heart, it is not surprising that an agent that affects sodium transport and membrane excitability has electrophysiologic effects on cardiac muscle. Diphenylhydantoin is effective in the treatment of arrhythmias following experimental myocardial infarction and in patients following heart surgery. Its most successful application has been in the treatment of arrhythmias believed to be due to digitalis intoxication (17). The experiments described in this report were designed to examine the effects of diphenylhydantoin on the electrophysiologic properties of the normal heart and to determine which of these effects could be attributed to a direct action on the myocardium and which to an indirect action through changes of cardiac autonomic nerve activity.

In normal awake dogs, diphenylhydantoin increased heart rate and shortened the conduction time across the A-V node. The increase in heart rate was observed in every dog, and the shortening of A-V conduction time was not dependent on changes of heart control ventricular rate. All of the dogs treated with diphenylhydantoin survived.

Diphenylhydantoin produced no significant changes of ventricular fibrillation threshold.
rate, since it was observed in dogs whose hearts were paced at a constant rate. Similar changes have been described by others (18).

Diphenylhydantoin has been reported to inhibit the action of acetylcholine on the myoneural junction (19) and to deplete the acetylcholine content of rat hearts after acute or chronic administration (20, 21). These findings suggest that it may have anticholinergic properties that could account, at least in part, for the changes of heart rate and A-V conduction observed in normal dogs. This view was supported by our findings that after total cardiac denervation, diphenylhydantoin failed to increase heart rate or A-V conduction. Indeed, following cardiac denervation it slowed sinus rate and A-V conduction. This observation suggests that its direct effect is a depressant one and may help to explain why other investigators (22) have found that high doses prolong the P-R interval of the electrocardiogram, even in normal dogs.

Changes of intraventricular conduction after diphenylhydantoin were evaluated by measuring conduction time in a segment of the Purkinje system (H-P interval) and an index of total ventricular activation time (H-S interval). Diphenylhydantoin produced either no change or only a slight prolongation of these intervals. Its failure to prolong intraventricular conduction is in marked contrast to the effects of certain other antiarrhythmic agents such as quinidine (23). The action of quinidine on conduction is thought to represent a reduction of available sodium carrier and a corresponding decrease in the rate of depolarization of myocardial cells (24). Diphenylhydantoin does not appear to have a similar effect on the penetration of sodium ion, at least in nerve fibers (25).

Diphenylhydantoin resulted in an increase in the amount of current that was required to produce a propagated response in either the atrium or the ventricle. This change in excitability was comparable to changes reported previously with quinidine at blood concentrations between 5 and 10 mg/liter (23). We have assumed in the past that the tissue beneath our chronically implanted recording electrodes was normal. This assumption was based on a constancy of conduction intervals over long periods and an absence of histologic evidence of injury. Our findings with diphenylhydantoin and the fact that other observers (7) have reported that it did not elevate the diastolic threshold of normal myocardium prompted us to look more critically at this problem. We found that unipolar tracings from electrodes chronically implanted on the epicardium almost always revealed an injury potential. This finding suggests that the tissue subjacent to the electrode was not normal. Our results may be ascribed to the fact that we were measuring the excitability of injured myocardium. Recent experiments by Gupta et al. (26) have shown that diphenylhydantoin elevates the diastolic threshold of ischemic myocardium without altering the excitability of normal muscle.

A significant reduction of the maximal rate at which the atria will respond to stimulation has been used as an index of the potential effectiveness of various agents in the treatment of rapid atrial arrhythmias (27). Diphenylhydantoin reduced the maximal atrial rate by approximately 25%. The decrease in maximal atrial rate could be an important factor in the ability of diphenylhydantoin to abolish atrial tachysystole induced by the local application of aconitine (3) and in converting atrial fibrillation or flutter to normal rhythm.

Woodbury (28, 29) has shown that diphenylhydantoin reverses the shortening of the action potential of ventricular muscle fibers produced by digitalis. We attempted to examine the action of diphenylhydantoin on digitalis-induced arrhythmias by taking advantage of the well-known effect of digitalis to facilitate the rhythmicity of the ventricular Purkinje fibers. Our results demonstrate that diphenylhydantoin is an effective antagonist of digitalis-facilitated pacemaker activity. Its effects on the excitability of atrial and ventricular muscle and on the maximal atrial rate in dogs that had not received digitalis suggest, however, that diphenylhydantoin has
antiarrhythmic properties that cannot be attributed solely to an antagonism of digitalis effects.

Until recently, the intravenous administration of diphenylhydantoïn for the treatment of cardiac arrhythmias has been considered to have a wide margin of safety. Ungar and Sklaroff (30) recently reported two fatalities following its intravenous use. Both patients had atrial flutter and died from ventricular systole within minutes after receiving diphenylhydantoïn. In one patient atrial flutter changed to normal rhythm and progressed rapidly to bradycardia and arrest. In the other, the degree of A-V block progressively increased and was followed by asystole. Both patients had severe heart failure. Diphenylhydantoïn apparently had a marked depressant effect on sinus pacemaker function in one, and on A-V conduction in the other. These responses resemble the changes produced by this agent in dogs whose hearts were depleted of their catecholamine stores following extrinsic denervation. Since chronic heart failure also leads to a decrease of the catecholamine stores in the heart (31), it seems reasonable to speculate that a heart that has lost some or all of its catecholamines, regardless of the cause, might be more sensitive to the depressant effects of diphenylhydantoïn. If this hypothesis is correct, it suggests that diphenylhydantoïn should be used with caution in the presence of severe heart failure.

Acknowledgment
The authors express their gratitude to Mr. James Manley, Mr. William Joyner and Miss Eleanor Timmerman for their assistance in this study.

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doi: 10.1161/01.RES.21.5.757

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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