Effects of Diphenylhydantoin on Atrioventricular Conduction in Man

By Richard H. Helfant, M.D., Sun H. Lau, M.D., Stafford I. Cohen, M.D., and Anthony N. Damato, M.D.

SUMMARY
The effects of intravenous diphenylhydantoin (5 mg/kg) on atrioventricular conduction in man at controlled heart rates in the digitalized and undigitalized state were studied. In undigitalized subjects, diphenylhydantoin administration consistently decreased A-V conduction time in each individual subject when identical heart rates were compared. Ouabain infusion produced an increase in A-V conduction time and this prolongation was always reversed by diphenylhydantoin. In two patients with atrial flutter and in two with atrial fibrillation, diphenylhydantoin caused a decrease in ventricular rate without affecting the atrial arrhythmias.

These findings are of clinical importance, especially in the therapy of digitalis toxicity. When digitalis excess is manifested by both ectopic beats and incomplete A-V block, diphenylhydantoin would have special utility since, in contrast with the commonly used antiarrhythmic agents, it decreases A-V conduction time in addition to suppressing ectopic beats. Diphenylhydantoin-induced depression of the ventricular rate in atrial flutter or fibrillation may also be useful clinically. However, since diphenylhydantoin markedly decreases ventricular automaticity, its use in patients with complete heart block is contraindicated.

Additional Indexing Words: Digitalis, Atrial pacing, Ouabain, Atrial flutter, Atrial fibrillation

DIPHENYLHYDANTOIN has been established as an effective cardiac antiarrhythmic agent¹-³ and clinical reports have indicated that it has special utility in the treatment of arrhythmias caused by digitalis excess.⁴-⁷ Animal studies have shown that diphenylhydantoin decreases ventricular automaticity while negligibly affecting intraventricular conduction.⁸ In addition, the drug has been shown experimentally to speed atrioventricular conduction.⁸ ⁹ Since the effects of diphenylhydantoin on conductivity have important clinical implications especially in the therapy of digitalis toxicity, the present study was undertaken to investigate its effects on atrioventricular conduction in man.

Methods
The results of 17 studies in 14 patients form the basis of this report. Ten normal male volunteers (mean age, 38 years) were studied in the postabsorptive, nonsedated state. None of these subjects were taking other prescribed medication, and all were in normal sinus rhythm. A tripolar electrode pacemaker catheter was inserted into an antecubital vein and positioned in the right atrium under fluoroscopic control. Leads I, II, V₁, and V₆ of a standard electrocardiogram and an intra-atrial electrogram were simultaneously monitored throughout each procedure. The right atrium was paced at rates of 100 to 150 beats/min with increments of 10 beats/min, using a battery-powered Medtronics pacemaker which delivered impulses of approximately 2 msec in duration at milliamperage of approximately twice threshold.

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Careful attention was paid to the grounding of all equipment. In all pacing studies, atrioventricular conduction time was measured from the pacemaker stimulus artifact to the beginning of the QRS complex. Measurements were made during periods of ventricular response to every atrial stimulus. All records were taken on a multichannel oscilloscopic recorder (Electronics for Medicine) at a paper speed of 100 mm/sec.

After control records were obtained, diphenylhydantoin (5 mg/kg) was infused intravenously at a rate of 50 mg/min. Right atrial pacing at the same rates as during the control period was repeated 2, 5, 15, and 30 minutes after completion of the diphenylhydantoin infusion.

In four subjects, the effects of diphenylhydantoin were studied after administration of digitalis. After control records during right atrial pacing were obtained as previously described, ouabain (500 mg) was infused intravenously, and the pacing studies repeated 5 and 20 minutes after completion of the infusion. Diphenylhydantoin (5 mg/kg) was then administered as above and the right atrium paced, 2, 5, 15, and 30 minutes after completion of the diphenylhydantoin infusion.

The effects of diphenylhydantoin in four patients with atrial arrhythmias are also included in the present study. Two of these patients were in atrial flutter and two in atrial fibrillation. After control resting electrocardiograms were recorded, diphenylhydantoin (5 mg/kg) was infused, and the effects were continuously monitored and recorded using lead II of the electrocardiogram. In 17 studies, blood pressure was monitored during diphenylhydantoin administration, either with a Courmand needle inserted into the brachial artery or with a conventional blood pressure cuff.

Results

Effect of Diphenylhydantoin on A-V Conduction

Heart rates were controlled in these studies since changes in sinus rate affect A-V conduction time\(^1\) and the drugs used in this study may affect sinus rate. In each subject, pacing the right atrium at increasing rates during the control period resulted in a progressive increase in the P-R interval (fig. 1). Diphenylhydantoin administration consistently produced a decrease in P-R interval in each individual subject from the control value 2 to 5 minutes after infusion, when identical paced heart rates were compared, and these changes persisted for the remainder of each study (table 1). However, the decrease in P-R interval tended to become less pronounced at the higher heart rates (fig. 1). At a paced heart rate of 100/min, the average decrease in P-R from control values was 54 msec, whereas at 140/min there was an average decrease of 24 msec. Both of these changes were highly significant (P < 0.001). Measurements of the QRS duration revealed no change after diphenylhydantoin administration in any subject studied at any paced heart rate. Side effects from diphenylhydantoin infusion consisted of pain at the injection site in two subjects and lightheadedness lasting less than 2 minutes in one subject. Systolic blood pressure decreased 10 mm Hg for less than 1 minute in one subject and was unaffected in nine patients.

Figure 1

A graphic summary of the effects of diphenylhydantoin on A-V conduction in undigitalized subjects. Pacing the right atrium at rates from 100 to 140 beats/min at increments of 10 beats/min resulted in a progressive increase in A-V conduction time from 219 to 262 msec (control). Five minutes after intravenous administration of diphenylhydantoin (DPH) (5 mg/kg) a decrease in A-V conduction time is produced when identical heart rates in the same individual are compared. At a heart rate of 100/min, the average A-V conduction time is 165 msec and at 140/min, 243 msec. Note that the decrease in A-V conduction tends to become less pronounced at the higher paced heart rates. The changes in A-V conduction time produced by diphenylhydantoin were stable throughout the remainder of each study.
### Table 1

**Effects of Diphenylhydantoin on Atrioventricular Conduction in the Normal Heart**

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Averages

| Control | 100 | 219 ± 7.2 | 110 | 237 ± 7.6 | 120 | 244 ± 6.8 | 130 | 252 ± 7.3 | 140 | 262 ± 7.1 |
| DPH | 100 | 165 ± 9.5 | 110 | 190 ± 7.5 | 120 | 212 ± 7.3 | 130 | 228 ± 7.7 | 140 | 243 ± 8.1 |

P < 0.001 < 0.001 < 0.001 < 0.001

**Abbreviations:** HR = heart rate; P-R = stimulus artifact to beginning of QRS (msec); DPH = effects of diphenylhydantoin (5 mg/kg) 5 minutes after administration; W = Wenckebach.

### Table 2

**Effects of Diphenylhydantoin on Atrioventricular Conduction in the Digitalized Heart**

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</table>

Averages

| Control | 100 | 216 ± 6.0 | 110 | 236 ± 8.6 | 120 | 247 ± 10.5 | 130 | 272 ± 10.7 |
| Ouabain | 100 | 245 ± 12.4 | 110 | 281 ± 15.4 | 120 | 289 ± 10.3 | 130 | 326 ± 12.6 |
| DPH | 100 | 208 ± 8.1 | 110 | 222 ± 10.8 | 120 | 235 ± 8.0 | 130 | 276 ± 11.4 |

P < 0.001 < 0.001 < 0.001 < 0.001

**Abbreviations:** HR = heart rate; P-R = stimulus artifact to beginning of QRS (msec); ouabain = effects of ouabain (0.5 mg given intravenously) 20 minutes after administration; DPH = effects of diphenylhydantoin (5 mg/kg given intravenously) 5 minutes after administration; W = Wenckebach.

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Effect of Diphenylhydantoin on A-V Conduction after Digitalis Administration

The effects of ouabain infusion on the P-R interval at various paced heart rates can be seen in table 2. In each subject, ouabain produced an increase in A-V conduction time above control values at all rates. At a rate of 100/min, ouabain produced an average increase in P-R interval of 29 msec ($P < 0.001$) and at 140/min of 46 msec ($P < 0.001$). Diphenylhydantoin administration resulted in a return of the P-R interval to the control value within 5 minutes in all cases. At a heart rate of 100/min, the average decrease in A-V conduction time was 37 msec ($P < 0.001$) and at 140/min, 50 msec ($P < 0.001$). Data obtained in this laboratory in subjects given ouabain (500 mg) alone and studied during atrial pacing indicate that this digitalis preparation progressively prolongs A-V conduction for at least 30 to 45 minutes. Experimentally ouabain exerts its effect on the A-V node for 2 hours. Therefore, in the current studies, diphenylhydantoin exerted its effect well within the duration of action of ouabain on A-V conduction. The changes observed 5 minutes after diphenylhydantoin infusion were quantitatively similar throughout the remainder of each study. In two subjects, diphenylhydantoin shortened the A-V conduction time below control values (fig. 2). QRS duration was unaffected by either digitalis or diphenylhydantoin in these subjects.

In these four subjects, the administration of both digitalis and diphenylhydantoin was accompanied by no adverse effects or subjective symptoms. There was no evidence of digitalis toxicity, such as ectopic beats, gastrointestinal upset, visual disturbance, or headache.

Effect of Diphenylhydantoin During Atrial Flutter and Atrial Fibrillation

The administration of diphenylhydantoin to two patients with atrial flutter and two with atrial fibrillation resulted in a decrease in the ventricular rate in all four patients. In one patient with atrial flutter, the ventricular rate decreased from 150 to 75 and this persisted for more than 2 hours. In the second patient with atrial flutter, the ventricular rate decreased from 120 to 80 following diphenylhydantoin administration (fig. 3), but this lasted only 1 hour. Both the rate and configuration of the atrial flutter waves were unaffected.

**Figure 2**

The effects of ouabain and diphenylhydantoin (DPH) on A-V conduction time, measured from the right atrial pacemaker stimulus artifact (St.) to the onset of the QRS complex (S-R). In the control period, pacing the right atrium at rates of 110, 130, and 150 beats/min causes progressive widening of the S-R interval. Ouabain (0.5 mg given intravenously) produces an increase in S-R interval at each paced heart rate 20 minutes after infusion. Diphenylhydantoin (5 mg/kg given intravenously) results in a shortening of the S-R interval beyond control values for each paced heart rate 5 minutes after infusion. These changes persisted for the remainder of the study. Paper speed is 100 mm/sec.
by diphenylhydantoin (fig. 3). In the two cases of atrial fibrillation, the ventricular rate decreased from 118 to 82 in one and from 96 to 78 in the other, and these changes persisted for more than 3 hours. The atrial fibrillation itself did not appear to be affected. All four patients were taking maintenance doses of digitalis prior to the time of the study, but none were clinically considered to manifest digitalis toxicity at the time of diphenylhydantoin administration, and all four patients tolerated diphenylhydantoin without incident.

**Discussion**

The results of this study indicate that in doses of 5 mg/kg diphenylhydantoin consistently produces a decrease in A-V conduction time (fig. 1). Since it has been shown that changes in heart rate affect atrioventricular conduction time, identical heart rates produced by atrial stimulation were compared in each subject (table 1). The dose of diphenylhydantoin used in this study has been found effective in treating arrhythmias clinically, and side effects were minor and transient.

Since several clinical studies have indicated that diphenylhydantoin has special utility in treating cardiac arrhythmias induced by digitalis, its electrophysiological properties at various levels of digitalization become important. Experimentally, diphenylhydantoin depresses ventricular automaticity, while having negligible effects on intraventricular conduction in the digitalis intoxicated and undigitzed heart. In addition it has been demonstrated in animal studies that diphenylhydantoin decreases A-V conduction time in the normal heart and completely reverses the A-V conduction prolongation induced by digitalis. The present findings regarding the effect of diphenylhydantoin on A-V conduction in man are consistent with those found experimentally. The intravenous administration of 0.5 mg of ouabain caused prolongation in A-V conduction in all cases (table 2). Diphenylhydantoin caused a prompt reversal of this prolongation, to control values in all cases and to below control values in two subjects (fig. 2). It should be noted that diphenylhydantoin caused no change in QRS duration in either the undigitzed or digitalized subjects. This observation confirms in man the experimental finding that diphen-
DIPHENYLHYDANTOIN AND A-V CONDUCTION

Phenytoin has no significant effect on intraventricular conduction.8 The administration of diphenylhydantoin to four patients with atrial flutter or atrial fibrillation caused a decrease in ventricular rate in all cases (fig. 3). Others have also reported that diphenylhydantoin decreased the ventricular rate in a patient with an atrial tachycardia4 and in a patient with atrial flutter.6

Direct studies of the electrical activity of the A-V node will probably be necessary to determine the exact mechanism of the effect of diphenylhydantoin on A-V conduction. Regardless of the mechanism involved, the effects of diphenylhydantoin on A-V conduction have important clinical implications, especially in the therapy of digitalis toxicity. Two of the most common electrocardiographic manifestations of digitalis excess are ectopic rhythms and A-V block of varying severity.12 Commonly used agents to suppress ectopic beats, such as potassium,13 procainamide,14 quinidine,15 and propranolol,16 may exacerbate the A-V conduction abnormality produced by digitalis. When digitalis toxicity is manifested by both ectopic activity and incomplete A-V block, diphenylhydantoin would have special utility since it can effectively suppress ectopia as well as decrease A-V conduction time. However, it is important at this point to emphasize that diphenylhydantoin is contraindicated in cases of complete heart block because the drug markedly depresses ventricular automaticity.9 Therefore, the initial manifestation of diphenylhydantoin in patients with complete heart block could be ventricular arrest.7 In addition, since none of the subjects in this study had organic disease of the A-V node, the effects of diphenylhydantoin in this setting are still to be ascertained.

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References
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