Protection from Digitalis Toxicity with the Prophylactic Use of Diphenylhydantoin Sodium

An Arrhythmic-Inotropic Dissociation

By Richard H. Helfant, M.D., Benjamin J. Scherlag, Ph.D., and Anthony N. Damato, M.D.

SUMMARY

Diphenylhydantoin sodium (Dilantin) given prophylactically increased the dose of digitalis necessary to produce toxicity by 72 to 224%. At constant heart rates, pretreatment with diphenylhydantoin sodium did not alter the elevation of rate of rise of left ventricular pressure produced by the glycoside.

Two implications have been drawn from these findings. First, the inotropic and arrhythmic actions of digitalis can be dissociated, since diphenylhydantoin sodium seems specifically to counteract the electrophysiological actions of the glycoside. Second, pretreatment with diphenylhydantoin sodium significantly widened the "toxic-therapeutic" ratio of digitalis. This, therefore, may have important clinical applications.

Additional Indexing Words:
Toxic-therapeutic ratio Acetylstrophanthidin Cardiac arrhythmia
Procaaine amide

In the digitalis-intoxicated heart, diphenylhydantoin sodium (Dilantin) has been shown to decrease ventricular automaticity without significantly impairing intraventricular conduction. These properties seem to account for the therapeutic effectiveness of diphenylhydantoin sodium as an anti-arrhythmic agent, particularly in the therapy of digitalis toxicity. The present study was undertaken to determine whether the prophylactic administration of diphenylhydantoin sodium could protect the heart against the electrophysiological manifestations of digitalis excess without interfering with the inotropic action of the glycoside. For comparative purposes, the dose of digitalis necessary to produce toxicity was determined after pretreatment with procaaine amide.

Methods

Ten adult mongrel dogs, weighing 11 to 25 kg, were anesthetized with sodium pentobarbital (30 mg/kg intravenously) and were subjected to each of the following procedures at weekly intervals in random order: (1) A single dose (7.5 µg/kg) of acetylstrophanthidin was injected intravenously followed by a continuous infusion of the drug (3 µg/kg/min) until a stable ventricular tachycardia was produced. (2) A single dose of diphenylhydantoin sodium (5 mg/kg) was administered intravenously over a 2-minute period. After 15 minutes, acetylstrophanthidin was administered as in (1). (3) A single dose of procaaine amide (30 mg/kg) was injected intravenously over a period of 2 minutes. After 15 minutes, acetylstrophanthidin was administered as in (1).

The animals were prepared in a similar manner for each experiment. The femoral vein was exposed and cannulated for infusion purposes. A Statham model SF 1 micromanometer catheter was positioned in the left ventricle by way of...
Table 1
Effect of Prophylactic Diphenylhydantoin Sodium and Procaine Amide on the Toxic Dose of Acetylstrophanthidin

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Dose of acetylstrophanthidin to produce toxicity (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alone</td>
</tr>
<tr>
<td>1</td>
<td>780</td>
</tr>
<tr>
<td>2</td>
<td>1000</td>
</tr>
<tr>
<td>3</td>
<td>1400</td>
</tr>
<tr>
<td>4</td>
<td>653</td>
</tr>
<tr>
<td>5</td>
<td>850</td>
</tr>
<tr>
<td>6</td>
<td>940</td>
</tr>
<tr>
<td>7</td>
<td>1110</td>
</tr>
<tr>
<td>8</td>
<td>1200</td>
</tr>
<tr>
<td>9</td>
<td>980</td>
</tr>
<tr>
<td>10</td>
<td>1185</td>
</tr>
</tbody>
</table>

Figure 1
Comparison of ventricular arrhythmias produced by (A) acetylstrophanthidin with no pretreatment, (B) acetylstrophanthidin after pretreatment with diphenylhydantoin sodium, and (C) acetylstrophanthidin after pretreatment with procaine amide. All procedures were carried out on the same animal on 3 different days (11/2, 11/9, and 11/16). Note that the ventricular arrhythmia induced by 9.4 mg of acetylstrophanthidin alone is similar to that produced by almost twice the dose of the glycoside after pretreatment with diphenylhydantoin sodium. In contrast, after pretreatment with procaine amide, 9.0 mg of acetylstrophanthidin induces a ventricular arrhythmia of an entirely different form.

The right or left common carotid artery. Left ventricular pressure (LVP) and the rate of development of LVP (dp/dt) were determined by use of an appropriate resistance-capacitance (RC) differentiating circuit. Lead II of the electrocardiogram was monitored continuously. Records were taken at 5 to 10-minute intervals and registered on an eight-channel switched beam oscillographic recorder.

In three animals, a bipolar electrode catheter, inserted into the right external jugular vein, was positioned against the lateral wall of the right atrium under fluoroscopic control. At 5 to 10-minute intervals, the atrium was paced at a fixed rate.
of 200 per minute. An AEL laboratory stimulator and isolation unit was employed to deliver driving impulses to the atrium at 20% above threshold intensity and 2.5 msec in duration.

Results
Effect of Prophylactic Diphenylhydantoin Sodium and Procaine Amide on the Toxic Dose of Acetylstrophanthidin

Table 1 lists the dose of acetylstrophanthidin which was required to produce a stable ventricular tachycardia (1) in the untreated heart and following the prophylactic use of (2) diphenylhydantoin sodium or (3) procaine amide.

When diphenylhydantoin sodium (5 mg/kg) was given prophylactically, the amount of acetylstrophanthidin necessary to produce toxicity (ventricular tachycardia) increased by 72 to 224%, the average increase being 122%. In contrast, the prophylactic administration of procaine amide (30 mg/kg) did not significantly alter the dose of acetylstrophanthidin required to produce toxicity (table 1).

In addition, it was observed that, in the same animal the acetylstrophanthidin-induced tachyarrhythmia exhibited different ventricular complexes when diphenylhydantoin sodium was used prophylactically than when procaine amide was used. In the diphenylhydantoin sodium studies, in all except one animal, the ventricular tachycardia which ultimately was produced by the increased amount of acetylstrophanthidin was electrocardiographically similar to that produced in the same animal by acetylstrophanthidin alone (fig. 1). With procaine amide plus acetylstrophanthidin, ventricular foci of varying forms and duration were produced. These beats alternated with nodal and fusion beats. Independent dissociated atrial activity was evident (fig. 1).

Effect of Prophylactic Diphenylhydantoin Sodium on the Inotropic Actions of Acetylstrophanthidin

In four of seven studies, diphenylhydantoin sodium (5 mg/kg) caused a transient decrease in the rate of rise of left ventricular pressure (dp/dt). However, dp/dt returned to control values in 1 to 15 minutes with an average time of 8 minutes. In three studies, there was no measurable change in the rate of rise of left ventricular pressure. The average maximum change in dp/dt due to diphenylhydantoin sodium, when it did occur, was 10% below control values.

The administration of acetylstrophanthidin 15 minutes after a single dose of diphenylhydantoin sodium caused a rise in dp/dt which was comparable in onset and degree of elevation to the rise observed when the glycoside was given alone (fig. 2). In all cases, the percentage increase in dp/dt was comparable at the same dose level of digitalis in each animal studied with or without prior administration of diphenylhydantoin sodium (table 2).

With acetylstrophanthidin alone, the maximum percentage increase of dp/dt was 16 to 44% with an average of 31.2%. After di-

Figure 2

Relationship between the log dose of digitalis and the per cent change in the rate of development of LV pressure (dp/dt) with acetylstrophanthidin alone (A.S.) and with acetylstrophanthidin after administration of diphenylhydantoin sodium (DPH). This representative study (dog 5, table 2) indicates that at a given dose level no significant difference is seen between the per cent elevation of dp/dt produced by acetylstrophanthidin with or without pretreatment with diphenylhydantoin sodium. In this case digitalis toxicity with acetylstrophanthidin alone occurred after 60 μg/kg; dp/dt at this dose was 31% above control values. After pretreatment with diphenylhydantoin sodium, acetylstrophanthidin toxicity occurred at a dose of 223 μg/kg and after a 56% change in dp/dt.
Table 2

Effect of Acetylstrophanthidin on Myocardial Contractility before and after Prophylactic Administration of Diphenylhydantoin Sodium

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Time after acetylstrophanthidin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 min HR dp/dt</td>
</tr>
<tr>
<td>3 a</td>
<td>100</td>
</tr>
<tr>
<td>b</td>
<td>120</td>
</tr>
<tr>
<td>4 a</td>
<td>130</td>
</tr>
<tr>
<td>b</td>
<td>160</td>
</tr>
<tr>
<td>5 a</td>
<td>130</td>
</tr>
<tr>
<td>b</td>
<td>150</td>
</tr>
<tr>
<td>6 a</td>
<td>180</td>
</tr>
<tr>
<td>b</td>
<td>150</td>
</tr>
<tr>
<td>7 a†</td>
<td>—</td>
</tr>
<tr>
<td>b</td>
<td>—</td>
</tr>
<tr>
<td>8 a†</td>
<td>—</td>
</tr>
<tr>
<td>b</td>
<td>—</td>
</tr>
<tr>
<td>9 a†</td>
<td>—</td>
</tr>
<tr>
<td>b</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: a = acetylstrophanthidin alone; b = acetylstrophanthidin administration begun 15 minutes after pretreatment with diphenylhydantoin sodium (5 mg/kg); and HR = heart rate.
*All dp/dt values are expressed as a percentage increase above control.
†In experiments 7, 8, and 9, heart rate was controlled at 200/min with right atrial pacing (see text).

Discussion

The results of the present study indicate that when diphenylhydantoin sodium is given prophylactically, the dose of digitalis necessary to produce toxicity is increased by 72 to 224%. In contrast, pretreatment with procaine amide did not protect against the development of digitalis toxicity. The variability of digitalis tolerance among animals was eliminated in the present study by having each animal serve as its own control for all experimental procedures.

The exact explanation for the observed differences between the protective action of diphenylhydantoin sodium and procaine amide is speculative. It has been shown that digitalis can cause ventricular arrhythmias by either increasing ventricular automaticity or prolonging intraventricular conduction. Diphenylhydantoin sodium in the dose ranges used has been shown to decrease ventricular automaticity without significantly affecting intraventricular conduction. Therefore, pretreatment with this drug should not affect the

Circulation, Volume XXXVI, July 1967

phenyldantoin sodium the same dose of acetylstrophanthidin increased the dp/dt an average of 30.5%. With increasing doses of acetylstrophanthidin given in the latter studies, the dp/dt continued to rise (fig. 2). The average peak increase of dp/dt with acetylstrophanthidin after diphenylhydantoin sodium was 50.5% above control values. In two dogs pretreated with procaine amide, the effect of acetylstrophanthidin on dp/dt was determined. Procaine amide caused an average maximum decrease in dp/dt of 42% below control which persisted after 15 minutes. The maximum increase in rate of rise of left ventricular pressure which could be achieved with acetylstrophanthidin before toxicity was only 3.6% above control values. In both procaine amide studies there was a marked and persistent elevation (10 to 20 mm Hg) of end-diastolic pressure. Diphenylhydantoin sodium administered prophylactically caused no significant change in end-diastolic pressure (0 to 5 mm Hg).
PROPHYLACTIC USE OF DIPHENYLHYDANTOIN SODIUM

action of digitalis on conduction but would increase the dose of digitalis necessary to cause arrhythmias due to enhanced automaticity. While the actions of procaine amide and diphenylhydantoin sodium on ventricular automaticity are qualitatively similar, procaine amide significantly increases intraventricular conduction. In addition, the combination of procaine amide and digitalis increases intraventricular conduction synergistically and this combination, therefore, tends to potentiate the development of "re-entry" arrhythmias. In this respect it is of interest that the character of the ventricular arrhythmias in the procaine amide studies differed from that produced when digitalis was given either alone or after pretreatment with diphenylhydantoin sodium. When procaine amide was given initially, digitalis produced a greater incidence of idioventricular complexes which varied in form and duration and alternated with nodal foci. When digitalis was given, alone or with diphenylhydantoin sodium, the form of the ventricular arrhythmia (with one exception) was always identical in each animal (fig. 1).

The effect of digitalis on the contractility of the heart has only recently been defined. Rushmer has found that ventricular contractility is accurately reflected by the rate of development of intraventricular pressure. Additional studies have clearly shown that digitalis increases the rate of rise of intraventricular pressure in the normal as well as the failing human heart.

In animal and human studies diphenylhydantoin sodium has been found to depress myocardial function only transiently. In the present study, it was found that if diphenylhydantoin sodium is given slowly, depression of left ventricular function is minimized and lasts no more than 15 minutes. Since the rate of rise of intraventricular pressure is affected by changes in heart rate, this variable was controlled with atrial pacing in three separate series of studies. The results clearly indicate that (at comparable heart rates) diphenylhydantoin sodium does not influence the effect of digitalis on the rate of rise of intraventricular pressure.

In each study the infusion of digitalis, started 15 minutes after diphenylhydantoin sodium, produced a progressive elevation of the rate of rise of intraventricular pressure comparable to that seen with digitalis alone (table 2). Therefore, the increase in myocardial contractility at each dose level of digitalis was not affected by pretreatment with diphenylhydantoin sodium. Indeed, since greater doses of digitalis were required to produce toxicity after prophylactic diphenylhydantoin sodium, the rate of rise of intraventricular pressure consistently surpassed the highest values which were obtained when digitalis was administered alone (fig. 2).

Although diphenylhydantoin sodium given prophylactically significantly increases the dose of digitalis necessary to produce toxicity, it does not inhibit the inotropic action of the glycoside. Two implications can be drawn from these findings: (1) It indicates that the inotropic and arrhythmic actions of digitalis can be dissociated, thereby providing a heretofore unavailable means of separately evaluating these two important actions of the glycoside. In this regard, it would appear that diphenylhydantoin sodium specifically antagonizes only the electrophysiological actions of digitalis and does not counteract the effects of the glycoside in a non-specific fashion. (2) These findings may have important clinical applications. Since pretreatment with diphenylhydantoin sodium increased the toxic dose of digitalis without affecting the dose at which positive inotropic effects occurred, the "toxic-therapeutic" ratio of the glycoside was markedly increased. If the combined use of diphenylhydantoin sodium and digitalis is shown to operate similarly in clinical situations, then patients who are very sensitive to the arrhythmic action of digitalis may be protected from its toxic effects while deriving its inotropic benefits.

Acknowledgment

We gratefully acknowledge the assistance of Anne Mazzella, Theresa Halloran, Audrey Pedersen, Joan
References


Franklin on Temperature Regulation of the Body—"Heat Stroke" 1758

"... our reapers in Pennsylvania, working in the open field in the clear hot sunshine common in our harvest time, find themselves well able to go through that labour without being much incommode by the heat while they continue to sweat, and while they supply matter for keeping up that sweat by drinking frequently of a thin evaporable liquor, water mixed with rum; but if the sweat stops, they drop, and sometimes die suddenly if a sweating is not again brought on by drinking that liquor, or, as some rather choose in that case, a kind of hot punch made of water mixed with honey and a considerable proportion of vinegar."—CARL VAN DOREN: Benjamin Franklin. New York, Viking Press, 1963, p. 279.
Protection from Digitalis Toxicity with the Prophylactic Use of Diphenylhydantoin Sodium An Arrhythmic-Inotropic Dissociation
RICHARD H. HELFANT, BENJAMIN J. SCHERLAG and ANTHONY N. DAMATO

Circulation. 1967;36:119-124
doi: 10.1161/01.CIR.36.1.119

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1967 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/36/1/119

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/