Cardioversion and Digitalis

IV. Effect of Beta Adrenergic Blockade

By Stephen M. Wittenberg, M.D., and Bernard Lown, M.D.

SUMMARY

Experiments were performed in anesthetized dogs to study some effects of propranolol, dextro-propranolol and ICI50,172 on digitalis-induced arrhythmias and digitalis-induced sensitization to electrical shock. When given in beta-blocking doses, propranolol did not abbreviate ouabain-induced ventricular tachycardia (VT) or decrease ouabain-induced sensitization to electrical shock. In larger doses, propranolol first controlled the arrhythmia without affecting shock sensitivity and then abolished both arrhythmia and shock sensitivity. Dextro-propranolol, a compound with nonspecific antiarrhythmic action equal to that of propranolol but with virtually no beta-blocking effect, abolished shock sensitivity, whereas ICI50,172, a pure beta-blocking agent, did not. Beta-blocking doses of propranolol given to dogs bordering on digitalis toxicity but in normal sinus rhythm caused recurrence of sustained ventricular tachycardia. Reappearance of toxicity appeared to be related to a propranolol-induced decrease in heart rate, since it was averted during continuous electrical pacing of the atrium and reversed by isoproterenol administration.

Additional Indexing Words:
Antiarrhythmic agents
Electrical countershock
Catecholamines
Ventricular tachycardia
Digitalis toxicity

dh

Patients bordering on digitalis toxicity may develop arrhythmias following cardioversion.1-3 Similarly, dogs after recovery from ouabain-induced ventricular tachycardia (VT), have a lowered threshold for electrically induced arrhythmias (fig. 1).4 The mechanism by which digitalis sensitizes the heart to electrical shock is unclear. Since catecholamines may act synergistically with digitalis in the production of arrhythmias,5-9 it is possible that electrical discharge releases stored catecholamines, thereby reinducing digitalis toxicity.

Beta-adrenergic blocking agents have been used to terminate digitalis-induced rhythm disturbances10-12 as well as to increase the threshold for the production of postcountershock arrhythmias in the digitalized animal.13 Many of these agents produce a nonspecific antiarrhythmic effect in addition to their capacity to induce beta-adrenergic blockade.14-17 Separation of their nonspecific from their beta-adrenergic effect is necessary to clarify how much of their efficacy is due to catecholamine antagonism.

Propranolol,18 its dextro-rotary isomer,15 and a new agent designated as ICI50,172 were used in studies on digitalis-induced sensitivity to electrical shock. The following questions were considered: (1) Does propranolol abolish shock sensitivity? (2) If it

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Before the administration of ouabain a 100 watt second (WS) shock does not evoke ventricular tachycardia (VT). However, after recovery from VT induced by 1,000 gamma ouabain a discharge of 0.2 WS re-evokes VT.

**Methods**

Fifty experiments were performed on mongrel dogs of both sexes weighing between 14 and 27 kg. The animals were anesthetized with sodium pentobarbital (30 mg/kg), intubated, and ventilated with room air by a Harvard respiratory pump. Defibrillator paddles 9 cm in diameter were covered with conductive paste and applied on either side of the shaved chest at the level of the apex thrust of the heart. Direct-current shocks, synchronized to fire on the QRS, were given to determine a control threshold for electrically induced ventricular tachycardia (VT). The latter was defined as the occurrence, within 15 seconds after shock, of four or more consecutive beats with aberrant QRS configuration and not in proper temporal relationship to a preceding P wave. An initial shock was delivered at 50 watt seconds (WS). If VT appeared, the energy was decreased to 25 WS; if VT did not appear, the energy was increased progressively from 100 WS to 400 WS in 100 WS increments. After determination of a control threshold all dogs were digitalized with ouabain to an end-point of VT. An initial dose of 700 μg was followed with increments of 100 μg at 10-minute intervals until toxicity appeared. Three types of experiments were then carried out.

In the first 20 experiments, dogs were given varying doses of propranolol, † as a bolus through

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*The instrument employed was the “Lown Cardioveter.”
†Propranolol was supplied by Dr. Alex Sahagian-Edwards of Ayerst Laboratories, New York, and dextro-propranolol and ICI50,172 by Dr. S. A. Stephen of Imperial Chemical Industries, Ltd., England.
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a jugular or saphenous venous catheter 5 minutes after the establishment of VT. Electrocardiograms were monitored continuously. After return to normal sinus rhythm (NSR), the electrical threshold for the production of VT was reetermined, starting with an energy of 0.2 WS. This had previously been found to be the median threshold after subsidence of digitalis-induced VT. If VT did not occur, serial shocks were given at 5, 10, 25, 50, and 100 WS until VT resulted.

In the second 25 experiments, dogs were permitted to recover from VT spontaneously. After resumption of NSR, the threshold to electrical shock was retested as in group one. If the sensitivity to electrical discharge was less than control, the dog was given propranolol, dextro-propranolol, or ICI50,172. Ten dogs received 0.2 mg/kg of propranolol. Besides exerting a nonspecific antiarrhythmic effect, this dose is known to produce beta blockade. Ten dogs received 0.2 mg/kg of dextro-propranolol. The latter exerts a nonspecific antiarrhythmic effect equal to that of propranolol, but is virtually free from beta-blocking action. Five dogs received 0.8 mg/kg of ICI50,172, a pure beta-blocking agent with a potency one third that of propranolol. Following drug administration, the threshold to electrical shock was retested in all dogs, starting with an energy of 0.2 WS.

Since the response to propranolol and ICI50,-

*Communication from Imperial Chemical Corporation, England.
†In five dogs studied in our laboratory a 5 mg/min infusion of isoproterenol resulted in an average increase in heart rate of 52.6 beats/min. After administration of 0.8 mg/kg of ICI50,172, the same dogs responded to a similar infusion with an average increase of only 16 beats/min.

172 in the above experiments appeared to be related to heart rate, five experiments were carried out at a fixed rate. In these studies animals received 0.2 mg/kg of propranolol immediately after spontaneous recovery from ouabain-induced VT. Their heart rates were held constant for 3 minutes after propranolol administration by pacing the atrium through a bipolar electrode catheter. The rate of stimulation was then reduced progressively until the dog's intrinsic pacemaker gained control. The electrocardiogram was recorded continuously from the time of propranolol administration to the emergence of the dog's intrinsic pacemaker.

Results

Effects of Propranolol during Ouabain-Induced VT

Although all animals received propranolol in a dose above that needed to produce 70 to 80% blockade of the beta receptors (0.15 mg/kg), abolition of digitalis-induced VT and post-VT shock sensitivity was dose-related. For the purpose of analysis, the animals were divided into three groups on the basis of their response to propranolol (table 1). Group I consisted of seven dogs in

‡The catheter was a U.S.C.I. #5651 driven by an American Optical pacemaker #10713A.
§No formal control group was studied. However, the group of 10 dogs cited in table 3 (in which VT was allowed to subside spontaneously and shock sensitivity was tested thereafter) serve adequately as a control. The median duration of VT was 67.6 ± 52 minutes, a result not significantly different from that of group I. The median energy threshold for the production of VT was 0.2-1 WS, the same as in group I.

Table 1

| Effect of Varying Doses of Propranolol on the Duration of Ouabain-Induced Ventricular Tachycardia (VT) and on the Median Energy Threshold for the Production of VT after Return to Normal Sinus Rhythm |
|---|---|---|
| Group | I | II | III |
| No. of dogs | 7 | 7 | 6 |
| Mean dose propranolol mg/kg | 0.25 ± 0.17* | 0.40 ± 0.17 | 0.63 ± 0.16* |
| Duration of VT (min) | 63.6 ± 10.1† | 7.6 ± 7.7† | 2.5 ± 3.7 |
| Energy threshold (WS) | 0.2-1.0 | 0.2-1.0 | 100 |

*†P < 0.01

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which neither VT nor post-VT sensitization to electrical shock was affected by drug administration. This group received a mean dose of 0.25 ± 0.17 (sd) mg/kg of propranolol. VT lasted for a mean duration of 63.6 ± 10.1 minutes and was followed by a median electrical sensitivity of 0.2-1 WS. Group II included seven animals receiving a mean dose of 0.4 ± 0.17 mg/kg of propranolol. VT was abbreviated to 7.6 ± 7.7 minutes, a duration significantly lower than that of the first group (P < 0.01). Post-VT shock sensitivity persisted at a level of 0.2-1 WS. Since no dog remained in VT longer than 16 minutes, a time span well below the 40 to 50 minute half-life of propranolol, shock sensitivity was present during virtually complete beta blockade.

Group III included the remaining six dogs, which received a mean dose of 0.63 ± 0.16 mg/kg of propranolol. VT was abbreviated, with a mean duration of 2.5 ± 3.7 minutes, and shock sensitivity was absent, with a median electrical sensitivity of 100 WS.

**Effects of Dextro-Propranolol, Propranolol, and IC150,172 after Spontaneous Recovery from Ouabain-Induced VT**

In the 10 animals receiving the dextro-isomer of propranolol (table 2), the electrical threshold for the production of VT was increased substantially in seven. Five animals were given a 5 μg/min infusion of isoproterenol and responded with a mean increase in heart rate of 41 beats per minute. This confirmed the absence of significant beta-adrenergic blocking action in the dextro-isomer.

### Table 2

**Effect of Dextro-propranolol (0.2 mg/kg), on the Energy Threshold for the Production of Ventricular Tachycardia Following Recovery from Ouabain Induced VT**

<table>
<thead>
<tr>
<th>Animal number</th>
<th>Threshold (WS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
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<tr>
<td>823</td>
<td>50.0</td>
</tr>
<tr>
<td>702</td>
<td>100.0</td>
</tr>
<tr>
<td>716*</td>
<td>100.0</td>
</tr>
<tr>
<td>716*</td>
<td>100.0</td>
</tr>
<tr>
<td>674</td>
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<td>U114</td>
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<tr>
<td>492</td>
<td>300.0</td>
</tr>
<tr>
<td>753</td>
<td>200.0</td>
</tr>
<tr>
<td>995</td>
<td>100.0</td>
</tr>
<tr>
<td>291*</td>
<td>100.0</td>
</tr>
</tbody>
</table>

*This number appears more than once throughout the tables since the same animal was used for more than one experiment. A recovery period of a few days was always allowed between experiments on the same animal.

### Table 3

**Effect of Propranolol (0.2 mg/kg), on the Energy Threshold for the Production of Ventricular Tachycardia (VT) Following Recovery from Ouabain-Induced VT**

<table>
<thead>
<tr>
<th>Animal number</th>
<th>Threshold (WS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>291*</td>
<td>100.0</td>
</tr>
<tr>
<td>695</td>
<td>400.0</td>
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<tr>
<td>U908</td>
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<td>401</td>
<td>200.0</td>
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<tr>
<td>476</td>
<td>50.0</td>
</tr>
<tr>
<td>291*</td>
<td>100.0</td>
</tr>
<tr>
<td>716*</td>
<td>100.0</td>
</tr>
<tr>
<td>720</td>
<td>200.0</td>
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<tr>
<td>12</td>
<td>400.0</td>
</tr>
<tr>
<td>457</td>
<td>400.0</td>
</tr>
</tbody>
</table>

*This number appears more than once throughout the tables since the same animal was used for more than one experiment. A recovery period of a few days was always allowed between experiments on the same animal.

†VT here indicates the development of ventricular tachycardia after 0.2 mg/kg of propranolol. The duration of VT is listed for each animal.
In the 10 animals receiving propranolol (table 3), it was possible to retest electrical threshold immediately in only four dogs. Two of these returned to control threshold after the initial 0.2 mg/kg of drug. The other two remained sensitive to an energy of 1 WS. The remaining six dogs redeveloped sustained ventricular tachycardia within 1½ minutes after propranolol was administered. These animals were monitored continuously until they had returned to normal sinus rhythm. Four of the five then tested displayed sensitivity to electrical discharges of 0.2-1 WS; the fifth returned to a threshold of 100 WS.

Of the five dogs receiving 0.8 mg/kg of ICI50,172 (table 4), only two could be tested for shock sensitivity immediately after drug administration. These two were still sensitive to energies of 0.2 and 1 WS, respectively. After administration of ICI50,172, the other three animals redeveloped sustained ventricular tachycardia, (a response similar to six of the animals receiving propranolol). After VT subsided, all three animals were sensitive to electrical shocks of 0.2-5 WS.

**Digitalis Toxicity Facilitated by Beta Blockade**

Continuous electrocardiographic recordings were obtained in five of the six dogs that redeveloped VT after the administration of propranolol. The appearance time of the VT ranged from 33 to 84 seconds after drug administration and averaged 49 seconds (table 5). The VT lasted between 12 and 60 minutes, with an average duration of 30 minutes. In every instance propranolol caused slowing of the sinus rate prior to the onset of VT (fig. 2). In three animals, 1 mg of atropine sulfate was given intravenously 3 minutes after the onset of VT. In one of these animals, there was a transient run of sinus tachycardia at a rate slightly higher than that of VT. In the other two, no change in rhythm or rate ensued. In these same three dogs, subsequent infusion of isoproterenol, 5 µg per minute, abolished the VT (fig. 3).

**Table 4**

*Effect of ICI50, 172 on the Energy Threshold for the Production of Ventricular Tachycardia (VT) Following Recovery from Ouabain-Induced VT*

<table>
<thead>
<tr>
<th>Animal number</th>
<th>Control</th>
<th>After ouabain</th>
<th>After ICI50, 172</th>
<th>After recovery from VT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A67</td>
<td>50.0</td>
<td>0.2</td>
<td>0.2</td>
<td>VT* (9 min) 5.0</td>
</tr>
<tr>
<td>549</td>
<td>50.00</td>
<td>1.0</td>
<td>1.0</td>
<td>VT (6 min) 0.2</td>
</tr>
<tr>
<td>A827</td>
<td>200.00</td>
<td>0.2</td>
<td>VT (16 min) 0.2</td>
<td></td>
</tr>
<tr>
<td>275</td>
<td>100.00</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>413</td>
<td>100.00</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*VT here indicates the development of ventricular tachycardia after 0.8 mg/kg of ICI50, 172. The duration of VT is listed for each animal.*

**Table 5**

*Redevelopment of Ventricular Tachycardia (VT) after Administration of Propranolol (0.2 mg/kg)*

<table>
<thead>
<tr>
<th>Animal number</th>
<th>Energy threshold (WS) after ouabain</th>
<th>Time of onset of VT after propranolol (sec)</th>
<th>Duration of VT (min)</th>
<th>Sinus rate before propranolol (beats/min)</th>
<th>Sinus rate after propranolol (beats/min)</th>
<th>Ventricular rate during VT (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>0.2</td>
<td>33</td>
<td>45</td>
<td>222</td>
<td>192</td>
<td>194</td>
</tr>
<tr>
<td>476</td>
<td>1.0</td>
<td>35</td>
<td>14</td>
<td>166</td>
<td>156</td>
<td>158</td>
</tr>
<tr>
<td>291</td>
<td>1.0</td>
<td>55</td>
<td>20</td>
<td>170</td>
<td>152</td>
<td>154</td>
</tr>
<tr>
<td>720</td>
<td>1.0</td>
<td>84</td>
<td>12</td>
<td>190</td>
<td>162</td>
<td>164</td>
</tr>
<tr>
<td>457</td>
<td>0.2</td>
<td>36</td>
<td>60</td>
<td>218</td>
<td>187</td>
<td>192</td>
</tr>
</tbody>
</table>

*Mean decrease in heart rate from propranolol was 23.4 beats/min.

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The isoproterenol was continued for 3 minutes, during which time the dogs remained in normal sinus rhythm. When the infusion was discontinued, all animals redeveloped VT.

**Prevention of Propranolol-Induced VT by Atrial Pacing**

None of the five animals given propranolol during continuous atrial pacing developed VT during the pacing. When the rate of stim-

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**Figure 2**

*After recovery from ouabain-induced VT the atrial rate is 170. Propranolol, 0.2 mg/kg, is administered intravenously. Fifty-five seconds later the atrial rate has decreased to 152 and a ventricular pacemaker has emerged at a rate of 154.*

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**Figure 3**

*The top tracing depicts propranolol-induced VT. Before starting isoproterenol the atrial rate is 139 and the ventricular rate 160. During isoproterenol infusion there is sinus node capture at a rate of 145.*
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After 2 min. Propranolol  Atrial Pacing 190

Sinus Rate 175

Atrial Pacing 164

Ventricular Rate 170

Figure 4

Following recovery from ouabain-induced VT the sinus rate is 175. Atrial pacing is begun at a rate of 190. Propranolol, 0.2 mg/kg, is administered intravenously. Although the dogs that were not paced developed VT within 1½ minutes, the dog shows no evidence of arrhythmia at 2 minutes. At 3 minutes the pacemaker is slowed and VT appears.

ulation was slowed, VT appeared in each animal (fig. 4). This was in contrast to the group of dogs that was not paced, in which six of 10 animals developed VT within 1½ minutes after propranolol.

Discussion

There were two stages of digitalis intoxication in the present studies: overt arrhythmia and latent arrhythmia exposed by electrical shock. Beta-blocking doses of propranolol given during VT did not effect the arrhythmia or the post-arrhythmia sensitization to electrical shock. By increasing the dose of propranolol it was first possible to terminate the arrhythmia without affecting shock sensitivity, and then to abolish both arrhythmia and shock sensitivity. These observations support previous studies implicating a nonspecific, dose-related antiarrhythmic effect in the abolition of digitalis-induced arrhythmias. This same nonspecific effect was apparently responsible for the abolition of arrhythmias produced by electrical shock. Separation of the two actions of propranolol supported this conclusion. Dextro-propranolol decreased sensitization to electrical shock.
without producing beta blockade; and ICI50,172 failed to affect shock sensitivity in spite of the production of beta blockade.

It is known that digitalis-induced arrhythmias may be facilitated by catecholamines. Becker and co-workers demonstrated that dogs given digoxin until they develop premature beats progressed to ventricular tachycardia and sometimes ventricular fibrillation when infused with isoproterenol. Conversely, the abolition of adrenergic influences sometimes protects from digitalis toxicity. Erlij and Mendez noted that a combination of adrenalectomy and sympathectomy increased the lethal dose of digitoxin in dogs and cats. In addition, Roberts and associates found that catecholamine depletion with reserpine diminished the number of ectopic beats induced by ouabain in cat papillary muscle, and Levitt and Roberts demonstrated that either catecholamine depletion with reserpine or beta blockade with pronethalol increased the amount of acetyl strophantidin required to produce ectopic escape beats after vagal stimulation in cats.

Recently, Ten Eick and associates showed that DCI, pronethalol, propranolol, n-isopropryl-p-nitrophenylethanolamine, reserpine and mediatinal neural ablation reduced the average number of ventricular ectopic beats produced by a countershock of given energy in normal and digitalized dogs. They concluded that post-countershock arrhythmias in dogs are partially dependent upon the release of norepinephrine. This stands in apparent contrast to the results of the present study. However, the studies are not completely comparable. Ten Eick and associates recorded ectopic beats after shocks primarily between 50 and 200 WS, and used 1 to 5 mg/kg of propranolol to reduce arrhythmia. Our endpoint was the appearance of ventricular tachycardia after a shock of 0.2 to 1 WS, and we used 0.2 mg/kg of propranolol to avert arrhythmia. The difference could therefore be due to the fact that ectopic beats produced by high-energy shocks are mediated through catecholamine action, whereas repetitive ventricular firing evoked by low-energy shocks is due to some other effect of digitalis on the heart. In addition, since Ten Eick's group used doses of propranolol well above those necessary for beta blockade, the "quinidine-like" effect of this compound offers another possible explanation for their results with this agent.

An unexpected observation during our studies was the recurrence of sustained VT in some digitalized animals receiving beta-blocking doses of propranolol or ICI50,172. This response was noted within 1.5 minutes after intravenous drug administration. In every instance the sinus rate slowed until a faster ventricular focus usurped as pacemaker. The dependence of this phenomenon on a decrease in atrial rate was supported by the observation that atrial pacing abolished the phenomenon. Furthermore, isoproterenol abolished the VT in the three dogs in which it was given, but only after increasing heart rate slightly. When isoproterenol was discontinued, rate slowed and VT reappeared. The experiments of Becker and co-workers are interesting in this regard. Of 5 dogs challenged with isoproterenol during incremental digitalization with ouabain, only three developed VT during isoproterenol in infusion. The remaining two developed arrhythmias 1½ minutes after isoproterenol was discontinued. Presumably the sinus rate was decelerating at this time.

The ability of vagal stimulation to unmask digitalis-induced ventricular ectopic activity is well known. However, to our knowledge, the appearance of digitalis toxicity as a side effect of sympathetic antagonism has not been previously described. Although it is impossible to extrapolate from animal experiments to a clinical setting, these studies make it reasonable to ask whether pure beta-adrenergic blockade can, by slowing the sinus rate, enhance rather than depress arrhythmias. The question also arises when severe digitalis toxicity is suspected whether it might be safer to use higher-than-usual doses of propranolol to ensure achieving the nonspecific, antiarrhythmic action of this agent.

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