Deleterious Effects of Bretylium in Cats with Digitalis-Induced Ventricular Tachycardia

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SUMMARY

The effect of bretylium on ventricular tachycardia induced by digitalis was studied in Dialurethane-anesthetized cats with continuous monitoring of the electrocardiogram and arterial blood pressure. Ventricular tachycardia was produced by repeated injections of deslanoside (25 μg/kg) at 15 min intervals. Only one of eight animals showed conversion of ventricular tachycardia to sinus rhythm with bretylium administration (2-100 mg/kg i.v.). In each animal, bretylium increased the ventricular rate. The effect of bretylium (30 mg/kg i.v.) on duration of ventricular tachycardia induced by deslanoside (0.75 μg/kg/min) was also studied. Duration was shortened from 65 ± 8.0 min to 7 ± 1.0 min, but the reduction was due to the intervention of either ventricular fibrillation or severe hypotension caused by bretylium. Pretreatment with propranolol (0.5 mg/kg i.v.) prevented these deleterious effects and unmasked an antiarrhythmic effect of bretylium since duration of ventricular tachycardia was significantly shorter (40 ± 6.0 min) than the controls (65 ± 8.0 min). In addition, an antiarrhythmic effect of bretylium was noted when it was administered as a dose of 30 mg/kg ip to animals 24 and 4 hours prior to deslanoside intoxication; 231 μg/kg Deslanoside were now required for inducing ventricular tachycardia as compared to 175 μg/kg deslanoside in controls. Thus, bretylium given alone during a digitalis-induced ventricular tachycardia increases both the rate of ventricular tachycardia and the likelihood of ventricular fibrillation. These deleterious effects appear to be related to a norepinephrine-releasing action and may be avoided by either pretreatment with propranolol or administration of bretylium several hours prior to digitalis intoxication.

Additional Indexing Words: Antiarrhythmic action Arrhythmogenic action Norepinephrine Ventricular fibrillation Neurodepression Propranolol Deslanoside

Several lines of evidence have appeared in the recent literature to indicate that the sympathetic nervous system plays an important role in the development of digitalis-induced ventricular arrhythmias. First, a positive correlation exists between the development of serious ventricular rhythm disorders produced by digitalis and excitation of the sympathetic nervous system produced by digitalis. Second, arrhythmias can be precipitated by either sympathetic nerve stimulation or administration of isoproterenol and norepinephrine in animals exposed to subarrhythmogenic doses of digitalis. Third, surgical interruption of sympathetic cardiac pathways protects the heart from otherwise cardiotoxic doses of digitalis. Fourth, conversion of digitalis-induced arrhythmias by drugs correlates with depression of digitalis-induced sympathetic neural hyperactivity. Fifth, drugs which normally counter digitalis arrhythmias fail to do so when the heart is deprived of sympathetic influence.

In view of the above observations we would anticipate that bretylium, a drug recommended as an important agent for the therapy of cardiac arrhythmias, would act as a “double edge sword” in the presence of ventricular arrhythmias produced by digitalis. We take this view because bretylium possesses opposing actions on the adrenergic nervous system. On the one hand, it exerts an antiadrenergic action by interfering with norepinephrine release from postganglionic sympathetic nerve endings. On the other hand, it releases norepinephrine from adrenergic nerve terminals and potentiates the effect of circulating catecholamines on adrenergic receptors.

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The purpose of our present study was to determine whether bretylium would exert a beneficial or harmful influence, or both, on ventricular arrhythmias induced by digitalis.

Methods

Cats of either sex with weights ranging from 1.6 to 3.2 kg were anesthetized with 0.6 ml Dial-urethane (Ciba) per kg administered by the intraperitoneal route. Tracheal cannulation was performed but all animals were allowed to breathe spontaneously. Polyethylene catheters were inserted into the femoral artery and vein for the purpose of measuring arterial blood pressure and administering drugs, respectively. The animal's body temperature was maintained between 36.5° and 38.5°C by warming with an infrared lamp. The electrocardiogram (lead II) and the arterial pressure were continuously recorded on a Beckman RB recorder.

Three types of experiments were performed to evaluate the effects of bretylium:

Type I. Deslanoside was administered in a dose of 25 µg/kg i.v. every 15 min to produce ventricular tachycardia. The criteria for ventricular tachycardia was a sustained idioventricular rhythm lasting at least 1 min and characterized by the presence of independent nonconducted atrial activity. After 1 min of ventricular tachycardia, bretylium was administered intravenously to test its capacity to convert deslanoside-induced ventricular tachycardia to sinus rhythm.

Type II. Deslanoside was infused at a constant continuous rate of 0.75 µg/kg/min until ventricular tachycardia of 3-min duration occurred. Digitalis infusion was terminated and bretylium, 30 mg/kg i.v., was administered to test its capacity to shorten the duration of an established ventricular tachycardia.

Type III. Deslanoside was administered as in the experiments of type I for the purpose of determining doses of deslanoside required to produce ventricular tachycardia and ventricular fibrillation in control animals and animals pretreated with bretylium (30 mg/kg i.v.) 24 and 4 hours prior to deslanoside intoxication.

The data were analyzed by paired comparisons and grouped Student t tests. The criteria for significance was P < 0.05.

Drugs used included Dial-urethane,* deslanoside,† propranolol hydrochloride,‡ and bretylium tosylate.§ Doses of drugs were calculated and administered as the salts.

Results

Bretylium was administered to eight animals in which ventricular tachycardia had developed from

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* Ciba Pharmaceutical Co, Summit, New Jersey.
† Gift from Sandoz Pharmaceuticals, Hanover, New Jersey, courtesy of Dr. Siegfried S. Wahrman.
‡ Courtesy of Ayerst Laboratories Inc., New York, New York.
§ Gift from Burroughs Wellcome Co, Research Triangle Park, North Carolina, courtesy of Dr. S. Bloomfield.

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the cumulative effects of 25 μg/kg deslanoside administered at 15 min intervals. Results obtained are summarized in table I. Only one animal was converted from ventricular tachycardia to a regular sinus rhythm. The other seven animals stayed in ventricular tachycardia and developed more serious rhythm changes with increasing doses of bretylium (fig. 1). Low doses of the drug (2–5 mg/kg) significantly increased the rate of the ventricular rhythm. The magnitude of the increase was 25.7 ± 6.7 beats/min. Higher doses (6–100 mg/kg) produced ventricular fibrillation in two animals and severe hypotension in five animals. The one animal that did convert to sinus rhythm did so because bretylium produced an “overdrive suppression” of abnormal pacemaker activity. That is, prior to bretylium administration, the rate of the ventricular tachycardia was 170 beats/min; after conversion with 3 mg/kg of bretylium, the reestablished sinus rate was 220 beats/min. Conversion lasted about 1.5 min. Additional bretylium (total dose of 47 mg/kg) resulted in ventricular fibrillation (fig. 2).

It was apparent from the above series of experiments that bretylium was generally ineffective as a treatment for ventricular tachycardia induced by deslanoside. Previous studies with other

Figure 1
Effects of bretylium on deslanoside-induced ventricular tachycardia. (A) Electrocardiogram (ECG) and arterial blood pressure (BP) tracings before intoxication with deslanoside. (B) Effects of a cumulative dose of 200 μg/kg deslanoside on ECG and BP, 1 min prior to ventricular tachycardia. (C) The deslanoside-induced ventricular tachycardia. (D) ECG and BP tracings 30 sec after 2 mg/kg bretylium was administered; note the increase in ventricular rate. (E) Tracings obtained 1 min after tracings of D and 30 sec after a total dose of 8 mg/kg bretylium; note the multifocal ectopic beats and the faster rate. (F) Tracings obtained 4.5 min after D and 1 min after a total dose of 18 mg/kg bretylium; note the brief period of ventricular fibrillation.
Effects of bretylium on deslanoside-induced ventricular tachycardia. (A) Electrocardiogram (ECG) and arterial blood pressure (BP) tracings before intoxication with deslanoside. (B) Effects of a cumulative dose of 175 µg/kg deslanoside on ECG and BP. 1 min prior to ventricular tachycardia. (C) The deslanoside-induced ventricular tachycardia. (D) ECG and BP tracings 30 sec after 3 mg/kg bretylium was administered. Note the conversion of ventricular tachycardia to rapid sinus rhythm.

Antiarrhythmic drugs such as diphenylhydantoin, diphenylthiohydantoin, propranolol, and clonidine showed that conversion of this rhythm disturbance to a normal sinus rhythm with a sinus rate less than the ventricular rate readily occurred when these drugs were administered. An explanation for the negative results obtained with bretylium in the arrhythmogenic model employed is that time is required for its antiarrhythmic action to develop. To test this possibility a slow, continuous infusion of deslanoside was used to produce the arrhythmia. Once the arrhythmia was established the infusion was stopped (after 3 min of ventricular tachycardia) and bretylium administered; no additional deslanoside was given. With this infusion technic, less overshoot in deslanoside dose occurred and spontaneous return of sinus rhythm was common. Most importantly, the duration of ventricular tachycardia was sufficiently long to allow for the effects of a slow-acting drug to occur.

Results obtained from the continuous infusion experiments are summarized in table 2. In control animals, i.e., animals in which bretylium was not administered, ventricular tachycardia developed after an average dose of 149 µg/kg deslanoside. Five of the nine control animals recovered from the...
Table 2

Effect of Bretylium Administration on Toxic Cardiovascular Changes Produced by Continuous Infusions of Deslanoside

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of experiments</th>
<th>Initial Mean BP (mm Hg ± s.e.)</th>
<th>Initial Heart rate (beats/min ± s.e.)</th>
<th>1 min before development of VT Mean BP (mm Hg ± s.e.)</th>
<th>1 min before development of VT Heart rate (beats/min ± s.e.)</th>
<th>1 min after onset of VT Mean BP (mm Hg ± s.e.)</th>
<th>1 min after onset of VT Heart rate (beats/min ± s.e.)</th>
<th>Approx 1 min after 30 mg/kg bretylium Mean BP (mm Hg ± s.e.)</th>
<th>Approx 1 min after 30 mg/kg bretylium Heart rate (beats/min ± s.e.)</th>
<th>Dose of deslanoside required to produce VT (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control*</td>
<td>9</td>
<td>116.0 ± 9.1</td>
<td>176.7 ± 9.3</td>
<td>100.8 ± 10.5</td>
<td>159.9 ± 11.0</td>
<td>92.2 ± 10.8</td>
<td>181.6 ± 13.0</td>
<td>-</td>
<td>-</td>
<td>149.1 ± 12.8</td>
</tr>
<tr>
<td>Bretylium</td>
<td>7</td>
<td>138.6 ± 7.6</td>
<td>174.8 ± 6.7</td>
<td>130.3 ± 14.2</td>
<td>181.8 ± 14.8</td>
<td>109.0 ± 14.2</td>
<td>207.7 ± 17.4</td>
<td>75.8 ± 6.0</td>
<td>222.8</td>
<td>132.1 ± 12.4</td>
</tr>
<tr>
<td>Bretylium pretreat</td>
<td>6</td>
<td>131.8 ± 10.2</td>
<td>198.0 ± 13.8</td>
<td>120.5 ± 10.6</td>
<td>125.8 ± 4.2</td>
<td>117.7 ± 8.0</td>
<td>165.0 ± 13.6</td>
<td>73.3 ± 12.6</td>
<td>170.8</td>
<td>146.3 ± 9.4</td>
</tr>
<tr>
<td>Propranolol pretreat</td>
<td>6</td>
<td>140.8 ± 9.7</td>
<td>194.2 ± 12.4</td>
<td>105.3 ± 9.2</td>
<td>138.2 ± 11.2</td>
<td>111.7 ± 7.3</td>
<td>154.0 ± 16.2</td>
<td>-</td>
<td>-</td>
<td>168.6 ± 14.5</td>
</tr>
</tbody>
</table>

*No bretylium.
†P < 0.05 with paired comparisons in reference to initial control values.
‡P < 0.05 with paired comparisons in reference to values obtained during ventricular tachycardia.

Abbreviation: VT = ventricular tachycardia.

Propranolol pretreatment alone did not significantly influence the duration of time spent in ventricular tachycardia. The duration of ventricular tachycardia was significantly greater (P < 0.05) for the propranolol-pretreated animals (6.2 ± 8.0 min) than for the control animals (6.5 ± 6.0 min). The remaining two animals were given propranolol alone (0.5 mg/kg). The propranolol was administered 40 ± 60 min after the onset of abnormalities due to deslanoside. The duration of ventricular tachycardia was significantly greater (P < 0.05) for the deslanoside-intoxicated animals (6.5 ± 6.0 min) than for the control animals (6.2 ± 8.0 min). A representative propranolol-pretreatment experiment illustrating the effects of a deslanoside-induced tachycardia is shown as Figure 4.

Another six animals that were to be given bretylium were pretreated with a dose of 1125 mg/kg deslanoside in a manner similar to that of the propranolol-pretreated animals. The remaining three died from ventricular fibrillation while the remaining three died from ventricular tachycardia. Four of the seven died from ventricular fibrillation while the remaining three died from ventricular tachycardia. Four of the seven died from ventricular fibrillation while the remaining three died from ventricular tachycardia. The fourth animal died from ventricular fibrillation. The average duration of the arrhythmia, when the dose was 720 ± 141 mg/kg, was 7.07 ± 141 min. This duration was significantly greater (P < 0.05) than that of the control animals (6.5 ± 6.0 min). Another six animals that were to be given bretylium were given propranolol (0.5 mg/kg). The propranolol was administered 40 ± 60 min after the onset of abnormalities due to deslanoside. The duration of ventricular tachycardia was significantly greater (P < 0.05) for the deslanoside-intoxicated animals (6.5 ± 6.0 min) than for the control animals (6.2 ± 8.0 min). A representative propranolol-pretreatment experiment illustrating the effects of a deslanoside-induced tachycardia is shown as Figure 4.
ventricular tachycardia. The ECGs of four of the six animals studied showed sinus rhythm at $74.0 \pm 14.5$ min after ventricular tachycardia had been initiated. The remaining two animals did not spontaneously convert; one animal fibrillated and the other animal was terminated after exhibiting a ventricular arrhythmia for 6 hours.

Pretreatment of animals with 30 mg/kg bretylium 24 and 4 hours prior to intoxicating them with deslanoside significantly increased the dose of deslanoside necessary to produce ventricular tachycardia (table 3). Pretreatment with bretylium also influenced the base blood pressure and heart rate as well as the effect of deslanoside on heart rate. After bretylium, cats had significantly lower heart rates and pressures to start with, and the usual bradycardia noted with deslanoside in control animals did not occur (table 3).

**Discussion**

The results of our study indicate that the antiarrhythmic drug, bretylium, may actually be arrhythmogenic if administered to cats with a ventricular tachycardia caused by digitalis. When
increasing doses of bretylium were given for the purpose of converting ventricular tachycardia to sinus rhythm, it increased the rate of the ventricular tachycardia, and in two cases, produced ventricular fibrillation. When a fixed dose of bretylium was given for the purpose of shortening the duration of an established ventricular tachycardia, it caused death in all animals tested. No animal survived more than 11 min after bretylium was administered while animals treated in the same way with digitalis but not given bretylium survived for an average of 72 min with eventual return to sinus rhythm occurring in more than half of the animals studied.

There have been three other reports which indicate that bretylium may be arrhythmogenic in the presence of digitalis. The two most impressive studies represent preliminary data. In the first, dogs intoxicated with ouabain were given bretylium (5 mg/kg i.v.), and in each case, bretylium increased the ventricular rate. In no instance did conversion to sinus rhythm occur. In the second, dogs intoxicated with acetylstrophanthidin to an endpoint of ventricular tachycardia were allowed 5 min

Figure 4

Effects of bretylium on deslanoside-induced ventricular tachycardia produced in propranolol-pretreated cats. (A) Electrocardiogram (ECG) and arterial blood pressure (BP) tracings before intoxication with deslanoside. (B) Effects of a cumulative infusion dose of 153 μg/kg deslanoside on ECG and BP. (C) Tracings obtained 3 min after tracings in B and 30 sec after 30 mg/kg bretylium. (D) Tracings obtained 3 min after tracings in C. (E) Tracings obtained 23 min after tracings in D; note restoration of abnormal rhythm to sinus rhythm.
### Table 3

**Effect of Bretylium Pretreatment on Cardiovascular Changes Produced by Deslanoside Intoxication**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of exp</th>
<th>1 min before development of VT</th>
<th>1 min after onset of VT</th>
<th>Dose of deslanoside needed to produce VT (μg/kg)</th>
<th>Mode of death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean BP (mm Hg ± SE)</td>
<td>Heart rate (beats/min ± SE)</td>
<td>Mean BP (mm Hg ± SE)</td>
<td>Heart rate (beats/min ± SE)</td>
</tr>
<tr>
<td>Control</td>
<td>10</td>
<td>122.6 ± 9.7</td>
<td>212.8 ± 7.8</td>
<td>96.5 ± 6.9</td>
<td>179.6 ± 12.5</td>
</tr>
<tr>
<td>Bretylium pretreat</td>
<td>4</td>
<td>74.0 ± 7.7</td>
<td>140.0 ± 13.5</td>
<td>64.8 ± 5.6</td>
<td>147.0 ± 15.0</td>
</tr>
<tr>
<td>(30 mg/kg ip 24 and 4 hours prior to exp)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05 with paired comparisons in reference to initial control values.
†P < 0.05 when compared to the corresponding value for the control group.
Abbreviations: VT = ventricular tachycardia; VF = ventricular fibrillation.

**Propensity for arrhythmogenesis:**
- Increased sympathetic nervous stimulation can produce effects similar to those produced by ergonovine.
- Increases in heart rate and cardiac output are seen with similar magnitude to those producing ventricular tachycardia.
- Bretylium administration increased heart rate in rats with ventricular tachycardia.
- These increases were not observed in animals without ventricular tachycardia.
- Bretylium administration was associated with increased sympathetic nervous stimulation.
- The mechanism for the adverse effect of bretylium is believed to be related to increased sympathetic nervous stimulation.

Bretylium-induced ventricular tachycardia was observed in rats with heart rates greater than 200 beats/min. The rate of its injection was 10-15 mg/kg/min. The rate of recovery from ventricular tachycardia was greater in rats pretreated with bretylium than in controls.

Bretylium injection in cats after the start of atrial fibrillation in cats with atrial fibrillation was associated with an increase in ventricular rate. The rate of recovery was greater in pretreated animals than in controls.

Bretylium was also found to be toxic in rats, producing ventricular tachycardia and fibrillation.

Bretylium-induced ventricular tachycardia was associated with increased sympathetic nervous stimulation and increased ventricular rate. The rate of recovery was greater in pretreated animals than in controls.

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Bretylium injection in cats after the start of atrial fibrillation was associated with an increase in ventricular rate. The rate of recovery was greater in pretreated animals than in controls.
effect. Thus, increases in heart rate, contractile force, and decrease in ventricular escape time occur immediately and become maximum in about 10 min after injection. Consistent with the postulate that bretylium-induced arrhythmogenesis is due to indirectly released norepinephrine is the fact that norepinephrine has the capacity to produce ventricular arrhythmias. In this regard, it has been reported by several investigators that catecholamines increase the sensitivity of the heart muscle to the toxic action of digitalis drugs. Conversely, digitalization increases the sensitivity of the heart muscle to the arrhythmogenic effect of catecholamines. Finally, either depletion of cardiac catecholamines with reserpine or blockade of beta-adrenergic receptors with propranolol prevents the positive chronotropic and inotropic effects of bretylium.

Based on the above findings, we felt that pretreatment with propranolol might protect the heart from the deleterious effects of bretylium. This was indeed the case since four of the six animals tested reverted from ventricular tachycardia to sinus rhythm after bretylium administration. Without propranolol pretreatment, six of six animals tested died within 11 min after bretylium administration. In summary, the arrhythmogenic effect of bretylium can be attributed to its indirect action of releasing endogenous catecholamines since the time-action curves for both effects are closely matched and blockade of the cardiac effects of released norepinephrine largely prevents arrhythmogenesis.

In addition to its sympathomimetic effects, bretylium blocks the release of endogenous norepinephrine by the nerve-action potential. The time-action curve for this effect is different than for the sympathomimetic effect. According to Kirpekar and Furchgott, partial blockade of the positive inotropic response resulting from sympathetic nerve stimulation occurs 15 min after drug administration with complete blockade occurring 45 min after drug administration. Similarly, Gilmore and Siegel have shown that the increases in coronary venous catecholamine output normally produced by sympathetic nerve stimulation do not occur 20 min after drug administration. Thus, the norepinephrine-releasing effect occurs early (immediately after injection) while the blockade of norepinephrine release occurs late (15–20 min after injection).

Since the sympathetic nervous system plays an important contributory role in the development of digitalis-induced ventricular arrhythmias, blockade of norepinephrine release by bretylium should help to counteract these arrhythmias. This was indeed the case since our results show that bretylium significantly shortened the duration of an established ventricular tachycardia of animals in which the early sympathomimetic effect of bretylium had been prevented by pretreatment with propranolol. Duration of ventricular tachycardia was 40 ± 6.0 min as compared to 65 ± 8.0 min for controls. The time period over which the antiarrhythmic effect was noted is consistent with the time period over which the blockade of norepinephrine release occurs. The possibility exists that the earlier return to sinus rhythm was not due to bretylium but was due to pretreatment with propranolol. To test this possibility, six animals pretreated with propranolol but not given bretylium were studied. Results obtained showed restoration to sinus rhythm 74 min after ventricular tachycardia was initiated. The time required was not significantly different than the time required for the controls but was significantly longer than the time required for the propranolol-pretreated animals treated with bretylium. Thus, the antiarrhythmic effect noted in the latter group was due to the bretylium and not to the propranolol.

To test further the influence of bretylium-induced sympathetic neurodepression on digitalis toxicity without exposing the digitalized heart to the initial period of bretylium-induced sympathomimetic effects, we administered bretylium alone to animals 24 and 4 hours prior to intoxicating them with deslanoside and determined the doses required for producing ventricular tachycardia. An antiarrhythmic effect was noted as a significantly larger dose of deslanoside was needed for inducing ventricular tachycardia as compared to controls. Similar results have been obtained by Papp and Vaughan Williams.

Our assumption that the antiarrhythmic mechanism of action of bretylium is due to its ability to block release of norepinephrine from cardiac sympathetic nerves agrees with the conclusions of Bassett and Hoffman. In their review of antiarrhythmic drugs, they state that “bretylium does not resemble either the quinidine-like drugs or DPH (diphenylhydantoin) and lidocaine in its effect on the relative magnitude of changes in effective refractory period and action potential duration. This fact, plus the failure of bretylium to decrease automaticity suggests that its antiarrhythmic efficacy in laboratory studies is not due to any intrinsic direct electrophysiologic effects.” Its antiarrhythmic
action may be exerted “through depression of neural function.” In a larger sense, evidence exists to support the view that bretylium, as well as other antiarrhythmic drugs, (e.g. diphenylhydantoin and propranolol) exert some of their antiarrhythmic effects through depression of neural function.1, 2, 9, 29, 30

In summary, our experiments demonstrate that bretylium has both arrhythmogenic and antiarrhythmic properties and both properties appear to be related to its effect on the sympathetic nervous system. This knowledge may be helpful in defining the role of bretylium in the therapy and prevention of cardiac arrhythmias. In the case of therapy for ventricular arrhythmias caused by digitalis, bretylium should be avoided especially by the intravenous route since worsening of the arrhythmia occurs.

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