Effectiveness of Bretylium Tosylate against Refractory Ventricular Arrhythmias

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SUMMARY
Thirty patients with ventricular tachyarrhythmias, which had not responded to intensive therapy with up to five antiarrhythmic drugs, were treated with bretylium tosylate. All patients had recurrent ventricular tachycardia, and 12 had repeated episodes of ventricular fibrillation. In 17 patients the arrhythmias followed acute myocardial infarction. Bretylium was administered intramuscularly or intravenously, and most patients received 4–5 mg/kg every 6 hours. Eighteen patients responded satisfactorily to bretylium and suffered no further ventricular tachyarrhythmias while receiving the drug. Bretylium partially suppressed ventricular arrhythmic activity in five patients and had no beneficial effects in seven patients. Administration of bretylium soon after the development of arrhythmias and withholding of other antiarrhythmic drugs during bretylium therapy favored a good antiarrhythmic response. Hypotension followed bretylium administration in 19 patients but exceeded 20 mm Hg in only one patient. Transient initial increases in blood pressure and ventricular arrhythmic activity occurred in five and four patients, respectively. Six patients were discharged from the hospital on oral bretylium 600 mg every 6 hours, and all have remained free from major ventricular arrhythmias for up to 15 months. In these patients postural hypotension was a transient and parotid pain a persistent side effect.

Additional Indexing Words:
Antiarrhythmic drugs Ventricular premature beats Therapy of arrhythmias
Myocardial infarction Ventricular fibrillation Oral bretylium tosylate
Ventricular tachycardia Postural hypotension Parotid pain

Bretylium Tosylate is a quaternary benzylammonium salt which is concentrated in postganglionic adrenergic nerves and interferes with their function.1–3 It was initially used as an antihypertensive drug,4 but was unsatisfactory for this purpose because of the rapid development of tolerance. The antiarrhythmic properties of bretylium were first recognized in 1965.5 Detailed studies by Bacaner then demonstrated the ability of bretylium to prevent, correct, and suppress electrically induced ventricular fibrillation in dogs.6–8 In two clinical studies on 309 and 3710 patients with major ventricular arrhythmias usually following acute myocardial infarction, bretylium was judged to be an effective and safe antiarrhythmic drug. It also appeared to prevent and suppress ventricular arrhythmias in 35 patients undergoing prosthetic valve surgery.11 Favorable effects have further been reported in seven of eight patients,12 in seven...
of 10 patients,\textsuperscript{13} and in two single cases\textsuperscript{14, 15} when bretylium was used after the failure of other antiarrhythmic drugs. Recently bretylium has been evaluated as a prophylactic drug against arrhythmias following acute myocardial infarction. In an uncontrolled study on 23 patients it was felt to be highly beneficial and superior to all other drugs as an antifibrillatory agent.\textsuperscript{10} In a controlled trial of 101 patients no significant effect on the incidence of ventricular arrhythmias was found, but supraventricular dysrhythmias were significantly reduced.\textsuperscript{16}

The mechanism of the antiarrhythmic action of bretylium has not been defined. It clearly differs from those of other antiarrhythmic agents.\textsuperscript{17, 18} The direct electrophysiologic actions of bretylium are limited to equivalent increases in action potential duration and effective refractory period. This suggests that at least part of its antiarrhythmic action is due to its effects on sympathetic nerve function.\textsuperscript{17, 18} These effects include interference with normal release of norepinephrine from nerve terminals, direct release of norepinephrine from nerve endings, and potentiation of the action of norepinephrine and epinephrine on adrenergic receptors by inhibiting catecholamine uptake into nerve endings.\textsuperscript{1, 3, 19–21} Which of these three effects predominate depends both on the concentration of bretylium and on the intensity of the existing sympathetic discharge.\textsuperscript{21} In the clinical situation the interactions of these effects are complex and their relative roles in the antiarrhythmic actions of bretylium in individual patients remain obscure.

During the past 16 months we have encountered 30 patients with serious ventricular arrhythmias unresponsive to lidocaine and other antiarrhythmic drugs. This report describes the effectiveness of bretylium tosylate in their treatment.

Patients and Methods

Thirty patients with serious ventricular arrhythmias refractory to intensive antiarrhythmic therapy with one to five antiarrhythmic drugs were treated with bretylium tosylate. All patients selected had suffered two or more bouts of ventricular tachycardia and showed persistent major ventricular ectopic activity during antiarrhythmic drug therapy. Fifteen patients had recurrent ventricular tachycardia requiring electroconversion while receiving full doses of two or three antiarrhythmic drugs. In 17 patients the arrhythmias treated with bretylium occurred after acute myocardial infarction; coronary artery disease without acute myocardial infarction was present in eight patients, coronary artery disease with ventricular aneurysm in three, cardiomyopathy in one, and postoperative aortic valve replacement in one patient. The mean age of the study population was 60.3 years, and there were 22 males and eight females.

When first treated with bretylium, all patients were hospitalized in intensive care units where their electrocardiograms were monitored continuously. After control of serious arrhythmias by bretylium, some patients continued to receive the drug in other hospital areas. All patients gave consent to the use of bretylium and remained under the care of their own cardiologists. The investigators acted as consultants and recommended that bretylium tosylate be given in a 5-mg/kg dose every 6 hours intramuscularly or intravenously over a 15-min period and that other antiarrhythmic drugs be withheld during bretylium therapy. These recommendations were usually followed, but doses and dosage intervals varied in some patients. Many patients received one or more antiarrhythmic drugs during the initial period of bretylium therapy. Decisions concerning discontinuation of bretylium therapy were also made by the cardiologist responsible for each patient's care, according to his evaluation of the clinical situation.

Several patients who had responded well to parenteral bretylium therapy subsequently received bretylium by mouth in 200-mg tablets, and six were ultimately discharged on oral maintenance therapy. After discharge all patients were initially seen at least once per week and after the first 2 months at biweekly or monthly intervals. During these follow-up visits each patient was carefully questioned concerning symptoms of arrhythmias, and a 5-min resting electrocardiogram was recorded.

A complete blood count, urinalysis, serum glutamic oxaloacetic transaminase, alkaline phosphatase, bilirubin, and creatinine or blood urea nitrogen were determined in all patients at the onset of bretylium therapy and at frequent intervals during therapy. In nine patients, 24-hour urinary excretion of epinephrine and norepinephrine was measured daily during parenteral treatment with bretylium.

Each patient's antiarrhythmic response to bretylium was classified in one of three categories:
(1) Good, if no further tachycardia or ventricular fibrillation occurred during treatment with bretylium.

(2) Partial, if there was a major reduction in ventricular arrhythmic activity or facilitation of electroconversion.

(3) None, if there was neither a quantitative nor a qualitative change in ventricular ectopic activity.

Results

Of the 30 patients treated with bretylium for serious and refractory ventricular tachyarrhythmias, 18 (60%) responded by having no further major ventricular arrhythmic activity while receiving bretylium therapy. Treatment with bretylium was partially successful in another five patients (17%). Only seven patients (23%) derived no apparent benefit from the drug. There was no correlation between the seriousness of the rhythm disturbance or the patients’ clinical state and the response to bretylium. Important characteristics of the patients grouped by categories of response are summarized in table 1. There were no significant differences among the three patient groups in age or sex distribution, percentage of patients with acute myocardial infarction, or mean bretylium dose. However, patients who showed a good response to bretylium generally received it sooner after the onset of their arrhythmias than the partial or nonresponders. Of the 18 patients who responded well to bretylium, 10 received the drug within 24 hours after serious arrhythmias first appeared; this was not true for any of the seven patients who failed to respond. Of the 12 patients who received bretylium more than 4 days after the onset of serious arrhythmias, only two responded satisfactorily, and six had no beneficial effect. Another factor which may have influenced the therapeutic effectiveness of bretylium was the concurrent administration of other antiarrhythmic drugs. Nine of the 18 patients in the good-response group received bretylium as the sole antiarrhythmic agent; this compares with only one of 12 patients in the two other groups. Patients whose arrhythmias were fully controlled by bretylium received a mean of 1.0 other antiarrhythmic drugs concomitantly; the other
patients received 2.0. Detailed data on each of the 30 patients treated are given in table 2.

**Good Response to Bretylium**

Seventeen of the 18 patients who responded well to bretylium did so after the first or second dose. Antiarrhythmic effects were usually apparent within 1 hour after parenteral injection, but complete and permanent suppression of ventricular arrhythmias was often delayed for several hours. Onset of action appeared to be faster after intravenous than after intramuscular injection. In most patients the antiarrhythmic effect of bretylium persisted during the entire dosage interval of 6–8 hours, but two patients required more frequent administration for complete suppression of arrhythmias.

Patient A.M. was unusual both in the delay and in the duration of her antiarrhythmic response. She had been unsuccessfully treated with diphenylhydantoin, lidocaine, procainamide, and propranolol for persistent ventricular bigeminy and recurrent ventricular tachycardia over an 11-day period and did not respond to the first four doses of 250 mg of bretylium. Twenty-four hours after diphenylhydantoin was discontinued, an intravenous injection of bretylium established normal sinus rhythm and maintained it for 3 hours. Each subsequent injection of bretylium promptly converted ventricular bigeminy to normal sinus rhythm, but bigeminy always returned within 2–3 hours.

Patient R.P. had recurrent ventricular tachycardia and persistent ventricular premature beats following an acute myocardial infarction despite combined therapy with diphenylhydantoin, lidocaine, procainamide, propranolol, quinidine, and transvenous ventricular overdrive pacing. When 300 mg of bretylium were injected intramuscularly during ventricular pacing, all ventricular ectopic activity disappeared within 30 min; 43 min after bretylium injection transvenous pacing was discontinued and no premature beats appeared. The patient was then maintained on parenteral bretylium every 6 to 10 hours for 28 days. Whenever an attempt was made to extend the dose interval beyond 10 hours, ventricular tachycardia recurred within 12 hours after the last dose of bretylium. The patient’s propensity to ventricular tachycardia was finally controlled by ventricular aneurysmectomy.

Patient J.W.B. had suffered repeated ventricular tachycardia and 10 episodes of ventricular fibrillation prior to bretylium therapy. He had no ventricular tachyarrhythmias during his first 3-day course of bretylium. Six hours after bretylium therapy was replaced by continuous infusion of lidocaine, ventricular premature beats reappeared and increased steadily in frequency. The second 3-day course of bretylium again suppressed all arrhythmic activity.

Six patients who had 10 or more episodes of ventricular tachycardia prior to being treated with bretylium showed no ventricular arrhythmic activity while receiving the drug but died prior to discharge. Patients M.C., T.D., and M.L. succumbed to unrelated noncardiac conditions. Patients G.P., J.P., and A.U. died from intractable ventricular arrhythmias 16, 18, and 33 hours after bretylium therapy had been discontinued. It seems possible that continued bretylium therapy might have prevented these deaths. Twelve patients who had responded well to parenteral bretylium were discharged with their ventricular arrhythmic activity under satisfactory control. Six of these patients received maintenance therapy with oral bretylium tosylate as described below. Six other patients were discharged on a variety of combinations of diphenylhydantoin, procainamide, propranolol, and quinidine.

**Partial Response to Bretylium**

In five patients injections of bretylium significantly reduced the frequency of ventricular premature beats and of episodes of ventricular tachycardia. However, arrhythmic activity was only partially controlled, and two of these patients ultimately died of ventricular fibrillation while still receiving bretylium. All five patients continued under treatment with lidocaine and other antiarrhythmic drugs after bretylium therapy was started. In all but one the dose of bretylium was less than 5
Summary of 36 Patients Treated with Bretylium

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age (yr), sex, weight (kg)</th>
<th>Diagnosis</th>
<th>Arrhythmias</th>
<th>Bretylium delay</th>
<th>Prior Rx</th>
<th>Concurr Rx</th>
<th>Bretylium dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. E.</td>
<td>39 M 75</td>
<td>CAD, VAn</td>
<td>VT, VPB</td>
<td>12 hours</td>
<td>D, L, P, Pp, Q</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>J.B.</td>
<td>25 M 80</td>
<td>MI</td>
<td>VT, VF, VPB</td>
<td>5 hours</td>
<td>D, L, P, Pp</td>
<td>D, L, P</td>
<td>4.4</td>
</tr>
<tr>
<td>J.W.B.</td>
<td>54 M 90</td>
<td>MI</td>
<td>VF, VT, VPB</td>
<td>3 hours</td>
<td>A, D, L, P</td>
<td>0</td>
<td>3.3</td>
</tr>
<tr>
<td>M.B.</td>
<td>73 M 84</td>
<td>CAD</td>
<td>VB, VT</td>
<td>24 hour</td>
<td>D, L, P, Q</td>
<td>0</td>
<td>3.8</td>
</tr>
<tr>
<td>M.C.</td>
<td>63 M 70</td>
<td>MI, CS</td>
<td>VT, VF</td>
<td>2 days</td>
<td>D, L</td>
<td>D, L</td>
<td>4.3</td>
</tr>
<tr>
<td>A.D.*</td>
<td>67 M 90</td>
<td>CAD</td>
<td>VT, VPB</td>
<td>24 hours</td>
<td>D, L, P, Pp, Q</td>
<td>0</td>
<td>3.3</td>
</tr>
<tr>
<td>T.D.</td>
<td>60 M 100</td>
<td>MI</td>
<td>VT, VPB</td>
<td>3 days</td>
<td>L, P</td>
<td>L, P</td>
<td>3</td>
</tr>
<tr>
<td>C.G.*</td>
<td>60 M 87</td>
<td>CAD, VAn</td>
<td>VT</td>
<td>12 hours</td>
<td>L, P</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>M.L.</td>
<td>57 F 90</td>
<td>CAD</td>
<td>VT, VF</td>
<td>2 days</td>
<td>D, L, P</td>
<td>D</td>
<td>3.3</td>
</tr>
<tr>
<td>A.M.</td>
<td>40 F 60</td>
<td>MI</td>
<td>VB, VT</td>
<td>11 days</td>
<td>D, L, P, Pp</td>
<td>D</td>
<td>5</td>
</tr>
<tr>
<td>A.C.M.*</td>
<td>70 M 80</td>
<td>MI</td>
<td>VT, VF, VPB</td>
<td>4 days</td>
<td>D, L, P, Pp, Q</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>G.M.</td>
<td>65 F 60</td>
<td>MI</td>
<td>VT, VF</td>
<td>7 hours</td>
<td>L, P</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>G.P.</td>
<td>63 M 80</td>
<td>MI, PE</td>
<td>VT, VF</td>
<td>3 days</td>
<td>D, L, Q</td>
<td>L</td>
<td>5</td>
</tr>
<tr>
<td>J.P.</td>
<td>66 M 80</td>
<td>MI</td>
<td>VF, VT</td>
<td>22 hours</td>
<td>D, L, P, Pp</td>
<td>D, L, P, Pp</td>
<td>3.8</td>
</tr>
<tr>
<td>R.P.</td>
<td>53 M 70</td>
<td>MI, VAn</td>
<td>VPB, VT</td>
<td>11 days</td>
<td>D, L, P, Pp, Q, EP</td>
<td>D, P</td>
<td>4.3</td>
</tr>
<tr>
<td>A.T.*</td>
<td>52 M 79</td>
<td>MI</td>
<td>VT, VF</td>
<td>2 hours</td>
<td>D, L, P, Q</td>
<td>L, P</td>
<td>5</td>
</tr>
<tr>
<td>A.U.</td>
<td>59 M 70</td>
<td>MI, PE</td>
<td>VT, VPB</td>
<td>3 days</td>
<td>L, P, Pp</td>
<td>0</td>
<td>4.3</td>
</tr>
<tr>
<td>R.V.*</td>
<td>54 M 70</td>
<td>CAD</td>
<td>VT, VF</td>
<td>24 hours</td>
<td>D, L, P, Q</td>
<td>0</td>
<td>4.5</td>
</tr>
</tbody>
</table>

*Patient discharged from hospital on oral bretylium therapy.

Abbreviations: AVR = postaortic valve replacement for aortic stenosis; CAD = coronary artery disease without acute myocardial infarction; CM = cardiomyopathy; CS = cardiogenic shock; MI = acute myocardial infarction; PE = pulmonary edema; VAn = ventricular aneurysm; (arrhythmias are listed in order of importance for each patient) VB = ventricular bigeminy; VF = ventricular fibrillation; VPB = ventricular premature beats ≥ 5/min; VT = ventricular tachycardia; bretylium delay = interval from onset of serious arrhythmias to start of bretylium therapy; Prior Rx = antiarrhythmic therapy before bretylium; Concurr Rx = antiarrhythmic therapy used concurrently with bretylium; A = alprostadil; D = diphenylhydantoin; L = lidocaine; P = procainamide; Pp = propranolol; Q = quinidine; EP = electrical pacing; 0 = none; BP = blood pressure; −1 = < 15-mm fall; −2 = 15-30-mm fall; +1 = < 15-mm rise; +2 = 15-30-mm rise; +3 = > 30-mm rise; B = bretylium tosylate; VA = ventricular arrhythmias.

mg/kg and its administration was delayed for more than 2 weeks after the onset of serious arrhythmias.

Bretylium abolished frequently recurring ventricular tachycardia requiring electrical countershock in patients D.C. and L.G., but each continued to have occasional episodes of up to six beats of ventricular tachycardia. Both patients were maintained on parenteral bretylium for 9 days and survived. Patient S.C. showed a definite decrease in ventricular premature beats during bretylium therapy but eventually died of irreversible ventricular fibrillation. Patient A.S. was being treated for...
BRETYLIUM TOSYLATE IN ARRHYTHMIAS

<table>
<thead>
<tr>
<th>Route</th>
<th>Dosage interval (hours)</th>
<th>Parenteral therapy (days)</th>
<th>BP</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.v., im</td>
<td>6</td>
<td>3</td>
<td>-2</td>
<td>No VT on B; alive</td>
</tr>
<tr>
<td>i.v., im</td>
<td>4-12</td>
<td>5</td>
<td>-1</td>
<td>No VT or VF on B; alive</td>
</tr>
<tr>
<td>im</td>
<td>6</td>
<td>6</td>
<td>-1</td>
<td>No VT or VF during 2 courses of B; alive</td>
</tr>
<tr>
<td>im</td>
<td>6</td>
<td>11</td>
<td>-2</td>
<td>No VA on B; alive</td>
</tr>
<tr>
<td>i.v., im</td>
<td>6</td>
<td>7</td>
<td>0</td>
<td>No VT or VF on B; died of sepsis and respiratory failure</td>
</tr>
<tr>
<td>i.v., im</td>
<td>8</td>
<td>7</td>
<td>-1</td>
<td>No VT on B; died after discharge of pulmonary embolism</td>
</tr>
<tr>
<td>i.v., im</td>
<td>8-12</td>
<td>12</td>
<td>-1</td>
<td>No VA on B; died of hepatic and renal failure</td>
</tr>
<tr>
<td>im</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>No VT on B; died after discharge of staphylococcal pneumonia</td>
</tr>
<tr>
<td>i.v., im</td>
<td>2-6</td>
<td>3</td>
<td>+3</td>
<td>B repeatedly converted VB to NSR for 2-3 hours; alive</td>
</tr>
<tr>
<td>i.v., im</td>
<td>6-8</td>
<td>10</td>
<td>-1</td>
<td>No VT or VF on B; alive</td>
</tr>
<tr>
<td>im</td>
<td>6</td>
<td>7</td>
<td>-1</td>
<td>No VA on B; alive</td>
</tr>
<tr>
<td>im</td>
<td>6</td>
<td>8</td>
<td>-1</td>
<td>No VT or VF on B; died from VA after B discontinued</td>
</tr>
<tr>
<td>i.v.</td>
<td>1 dose</td>
<td>1</td>
<td>0</td>
<td>No VT or VF on B; died from VA after B discontinued</td>
</tr>
<tr>
<td>i.v., im</td>
<td>6-12</td>
<td>28</td>
<td>-1</td>
<td>No VA on B; underwent aneuryssectomy; alive</td>
</tr>
<tr>
<td>im</td>
<td>6-8</td>
<td>6</td>
<td>-1</td>
<td>No VA on B; alive</td>
</tr>
<tr>
<td>i.v., im</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>No VA on B; died from VA after B discontinued</td>
</tr>
<tr>
<td>im</td>
<td>6-8</td>
<td>5</td>
<td>+1</td>
<td>No VT or VF on B; died after discharge during cardiac surgery</td>
</tr>
</tbody>
</table>

A. Good response to bretylium (n = 18)

B. Partial response to bretylium (n = 5)

C. No response to bretylium (n = 7)

Cardiogenic shock with epinephrine and isoproterenol when bretylium therapy was started because of frequent ventricular premature beats and recurrent ventricular tachycardia. Bretylium reduced the requirement for catecholamines and the overall ventricular arrhythmic activity, but the patient died on the second day of shock and ventricular fibrillation. In H.S. the first dose of bretylium converted ventricular tachycardia to normal sinus rhythm. However, minor arrhythmic activity continued, and the patient died of ventricular fibrillation 18 hours after his last dose of bretylium.

No Response to Bretylium

Of the seven patients who did not respond to bretylium, all but one received the drug at least 1 week after the onset of serious arrhythmias. The one exception, A.B., had severe cardiogenic shock following acute myocardial infarction and had required DC countershock on more than 50 occasions before receiving bretylium. Of the six other patients, five were treated with full doses of lidocaine and procainamide concomitantly with bretylium, and four were given diphenylhydantoin as well. Patient B.M. received only a single dose of bretylium, R.S. only two, and
A.B. and A.I. only three doses. Patients G.B. and E.S. were the only two patients who received each dose of bretylium by intravenous infusion given over a 2-hour period. It is likely that this method of administration produces lower peak levels of bretylium in the myocardium and may therefore be less effective than intramuscular or more rapid intravenous injection.

Side Effects
Side effects observed during 1–28 days (mean 6.3 days) of parenteral bretylium therapy are listed in table 3. Hypotension was by far the most common untoward effect and occurred to some degree in two thirds of all patients within 1 hour after injection. After the first dose of bretylium hypotension often appeared earlier than the antiarrhythmic action. Since the fall in blood pressure in the recumbent position was less than 20 mm Hg in 29 of 30 patients, it was of little clinical importance. In only one patient (B.M.) was parenteral bretylium therapy discontinued because of hypotension which lasted several hours. There was no correlation between the dose of bretylium and the amount of blood pressure reduction.

Five of the 30 patients showed hypertensive responses to parenteral bretylium during the first hour after injection. The hypotension in patient B.M. was preceded by a transient 15-mm Hg rise in blood pressure. Patient R.V. showed transient 10–15-mm Hg increases in blood pressure after parenteral doses of bretylium, but these were not seen during his later oral therapy. Asymptomatic blood pressure elevations of up to 50/20 mm Hg occurred in patients A.I. and L.G. about 1 hour after each intramuscular injection of bretylium. Patient A.M. showed no change in blood pressure during the first 24 hours of parenteral bretylium therapy, but during the next 2 days each dose was followed by a hypertensive response of up to 69/30 mm Hg associated with headache and an aching, heavy sensation in the legs. Because of these symptoms bretylium therapy was discontinued after 3 days.

In four patients each parenteral dose of bretylium led to an initial transient increase in ventricular arrhythmias. Patients D.C., J.M., and A.I. showed only a slight increase in the frequency of ventricular premature beats during the first hour after bretylium. In D.C. this was followed by suppression of these rhythm disturbances. In patient A.S. some injections of bretylium led to a marked enhancement of premature ventricular beats and to short runs of ventricular tachycardia. This patient was receiving intravenous epinephrine and isoproterenol, and bretylium injections produced a fourfold potentiation of the hemodynamic effect of this infusion. It appears likely that the unusual increase of ventricular arrhythmias by bretylium in this patient was related to its administration during infusion of catecholamines.

Only three patients became nauseated during parenteral bretylium therapy. In A.C.M. nausea and vomiting occurred only after the first intravenous dose. Patient R.P. had nausea and vomiting following the first intramuscular dose and whenever intravenous administration was rapid. Patient M.C. was slightly nauseated throughout bretylium therapy but did not vomit. Patient D.C. developed transient involuntary vertical head shaking following each bretylium dose which coincided with a transient increase in ventricular premature beats. Parenteral bretylium therapy had no apparent adverse effects on hematologic, hepatic, or renal function in any patient. Administration of bretylium had no apparent effect on urinary excretion of norepinephrine or epinephrine. There was no
significant difference in the urinary catecholamine excretion between patients who did or did not respond satisfactorily to bretylium.

**Oral Bretylium Therapy**

Six patients whose recurrent episodes of ventricular tachycardia or fibrillation had been eliminated by parenteral bretylium therapy were maintained on oral bretylium after discharge. Oral therapy was started with a dose of 600 mg bretylium tosylate. This dose is twice the common parenteral dose and was chosen because bretylium is incompletely absorbed from the gastrointestinal tract. During the first 48 hours, oral doses of 600 mg were alternated every 6 hours with each patient's former parenteral dose. If control of arrhythmic activity remained satisfactory on this regimen, the patient was then placed on 600 mg orally every 6 hours. If the therapeutic response was not satisfactory, the oral dose was increased by 200-mg steps until arrhythmias were controlled or until intolerable postural hypotension developed. Such an increase was necessary in only one patient (M.B.). Despite her excellent response to parenteral bretylium, this patient's ventricular arrhythmias were not controlled even with 1 g oral bretylium every 6 hours. She developed marked postural hypotension on that dosage, and bretylium was discontinued. The six patients who were successfully maintained on oral bretylium therapy were all taking 600 mg every 6 hours when discharged from the hospital.

Clinical data on the six ambulatory patients treated with oral bretylium are included in table 2. There has been no evidence of recurrence of major ventricular arrhythmias in any of these patients during oral bretylium therapy. Three patients (A.D., C.G., and R.V.) have died from unrelated conditions after 1-3 months of successful antiarrhythmic therapy with oral bretylium. Three other patients (H.B., A.C.M., and A.T.) are doing well after 10-15 months of such therapy. Patient H.B. had suffered 10 attacks of ventricular tachycardia during the 2 months before bretylium therapy, had been hospitalized for 4 weeks, and had not responded to various combinations of five antiarrhythmic agents. During 12 months of oral bretylium therapy he has had only rare and isolated ventricular premature beats and has resumed a physically active life. Whenever withdrawal of bretylium has been attempted, serious ventricular arrhythmias have promptly developed. Patient A.C.M. had recurrent ventricular tachycardia and fibrillation prior to being treated with bretylium. Since starting oral bretylium 15 months ago he has shown only rare ventricular premature beats. He plays golf and leads a normal life. Patient A.T. has been free of all ventricular arrhythmic activity during 10 months of oral bretylium therapy and has resumed work as an attorney.

Five of the six patients had mild postural hypotension during the first 2 weeks to 2 months of ambulatory treatment with oral bretylium. This was always transient and presented no problems. All three surviving patients have had persistent parotid pain which appeared after 2-4 months of bretylium therapy. This pain occurs only during eating, particularly with the first meal of the day, but is intense and is increased by mastication. It is associated with increased salivation but not with swelling or inflammation of the parotid gland or duct. This complication of chronic bretylium therapy has been distressing but has not required the withdrawal of the drug in these patients at high risk of serious arrhythmias.

**Discussion**

Our experience with bretylium tosylate strongly suggests that it is a commonly effective drug for the control of serious ventricular arrhythmias in patients refractory to other antiarrhythmic agents. During parenteral administration of bretylium for periods of 1-28 days no further ventricular tachycardia or fibrillation occurred in 18 of 30 patients who had suffered from frequently recurring, serious ventricular tachyarrhythmias. No patient in this group died from ventricular arrhythmias while receiving bretylium, and the clinical course of several patients suggests strongly that the effect of bretylium was
lifesaving. This favorable response is particularly striking in view of the failure of these 18 patients to respond satisfactorily to vigorous therapy with many other drugs. Unsuccessful administration of two to five (mean 3.8) such drugs singly and in combination for periods ranging from 3 hours to 11 days had preceded the start of bretylium therapy.

Results of uncontrolled studies on antiarrhythmic drugs must be interpreted with caution. Spontaneous variations in the nature and frequency of ventricular arrhythmias are notorious, and the failure of an arrhythmia to recur during administration of a drug cannot automatically be credited to that drug. This is particularly true in patients with acute myocardial infarction whose risk of ventricular arrhythmias decreases progressively. Nevertheless, temporal relationships between start and end of drug administration and occurrence of arrhythmias as well as other details of the clinical course can go far toward establishing a beneficial role of the drug. There was little doubt in any of the 18 patients described as responding satisfactorily to bretylium that this drug was actually responsible for the observed suppression of recurrent ventricular tachyarrhythmias. None of these 18 patients died from arrhythmias during bretylium therapy, while five of the 12 patients whose response to bretylium was unsatisfactory died arrhythmically. Three patients who responded well to bretylium died of ventricular fibrillation within 2 days after bretylium therapy was stopped.

In this series bretylium controlled life-threatening ventricular arrhythmias in the majority of patients who did not respond satisfactorily to lidocaine and multiple other antiarrhythmic drugs. This does not indicate that bretylium is the most effective drug for therapy of serious ventricular arrhythmias. If bretylium were used as a first drug, a similar percentage of nonresponders to bretylium might be found to respond to other antiarrhythmic agents. The question can only be answered by controlled studies comparing bretylium with other antiarrhythmic drugs in well-defined populations. Failing such studies bretylium cannot yet be considered the agent of first choice for treatment of ventricular arrhythmias. On the other hand, a trial of bretylium seems indicated whenever serious ventricular arrhythmias fail to respond to optimal lidocaine therapy. It no longer appears reasonable to delay bretylium therapy for several days after the ineffectiveness of various combinations of diphenylhydantoin, lidocaine, procainamide, propranolol, and quinidine has become apparent.

In this study a long interval between the onset of major arrhythmias and the start of bretylium therapy was associated with an unsatisfactory response to bretylium. The administration of other antiarrhythmic drugs concomitantly with bretylium appeared to have a similar effect, since 90% of patients who received no other drugs responded well to bretylium while only 45% showed a good response when given other antiarrhythmic drugs concurrently. Interference by other drugs with the action of bretylium has also been observed by others. In a previous study, patients whose arrhythmias were not satisfactorily suppressed with a bretylium dosage of 5 mg/kg every 6–8 hours commonly responded when the dose was increased or the dosage interval was reduced. This suggests that arrhythmias in some of the 12 patients in our series whose response to bretylium was unsatisfactory might have been controlled if a higher dosage had been administered. However, the dose-response relationship for bretylium requires further study. No characteristics of patients or of ventricular arrhythmias which might have influenced the antiarrhythmic effectiveness of bretylium became apparent. At this time the response of individual patients with serious ventricular arrhythmias to bretylium cannot be predicted any more than their response to other antiarrhythmic drugs.

The mechanisms of the antiarrhythmic action of bretylium remain uncertain. The effectiveness of bretylium against ventricular arrhythmias is often attributed to its ability to block sympathetic stimulation of the myocardiun, but there is no direct evidence for this.
view. In this study there was no clinical or laboratory evidence that the 18 patients who responded well to bretylium had unusually intense sympathetic activity which might have played an important role in the genesis of their arrhythmias. Actually, the effects of bretylium on sympathetic function are quite complex and depend both on its concentration and on the preexisting rate of sympathetic discharge.21

In addition to blocking the release of norepinephrine by the sympathetic nerve action potential, bretylium itself releases norepinephrine from sympathetic nerve endings in the myocardium.18, 21 At high concentrations the latter effect predominates.21 Plasma concentrations of bretylium can fall into this range during its therapeutic use.29 Release of norepinephrine from cardiac sympathetic nerves is responsible for the positive chronotropic, dromotropic, and inotropic effects of bretylium.17, 18, 20, 21

Furthermore, in contrast to propranolol, bretylium does not block the action of circulating norepinephrine and epinephrine on the myocardium. In fact, it potentiates the myocardial actions of these catecholamines, though not that of isoproterenol, by blocking their uptake into nerve endings.10-21 The varied abilities of bretylium to depress physiologic release of norepinephrine, to release norepinephrine, and to potentiate locally released and circulating norepinephrine and epinephrine are opposing drug actions whose net effect in a given patient is impossible to predict. However, all these actions could increase the homogeneity of adrenergic stimulation of the myocardium and this may exert antiarrhythmic effects. The action of bretylium differs from the effect of beta-adrenergic antagonists which reduce the cardiac actions of catecholamines but do not eliminate local differences in adrenergic drive unless they block it completely. Finally, the antiarrhythmic action of bretylium may in part be due to its direct electrophysiologic action on the myocardium. The drug increases the action potential duration and effective refractory period of both ventricular muscle and Purkinje fibers.17, 18

The cardiovascular side effects of bretylium almost certainly result from its action on the sympathetic nervous system. Some degree of hypotension due to the adrenergic blocking action of the drug was seen in most patients but was largely postural. In only one patient did recumbent hypotension exceed 20 mm Hg and lead to discontinuation of bretylium therapy. However, concern about a possible increase in hypotension limited the doses administered to other patients. It appears doubtful that such concern was justified, since the degree of hypotension was not related to dosage in our series and since others have found hypotension to be more common and marked with low doses of bretylium.16 Temporal dissociation between the hypotensive and the antiarrhythmic action of bretylium was common, suggesting that the latter may have mechanisms other than adrenergic blockade. Initial, transient hypertension in some patients was almost certainly due to the release of norepinephrine from sympathetic nerve endings by high concentrations of bretylium which then increases myocardial contractility, cardiac output, and peripheral resistance.21, 24, 25 The expected increase in frequency of initial hypertension with higher doses of bretylium was not apparent in this series.

Although hypotension and hypertension are both potentially dangerous in patients with ischemic heart disease, the limited blood pressure changes observed during this study had no apparent ill effects on any patient. The transient increases of ventricular arrhythmic activity shortly after parenteral injection of bretylium which appeared in four patients during this study and the slight cardioacceleration and improvement of A-V conduction not seen in this series but found by others in occasional patients9-11 can also be attributed to norepinephrine release.17, 18

Experience with chronic administration of oral bretylium is still quite limited.9, 15 We had encouraging results in three patients who have been maintained free of major arrhythmias
during 1 year of oral bretylium therapy after other oral antiarrhythmic agents had failed. It is of interest that in these patients tolerance developed rapidly to the hypotensive effects of bretylium but not to its antiarrhythmic action. This finding again raises the possibility that at least part of the antiarrhythmic action of bretylium is independent of its adrenergic blocking action.

Acknowledgments
We thank Barbara Noel, R.N., and Mrs. Susan Boehmke for valuable technical assistance and Dr. Stanley T. Bloomfield of Burroughs-Wellcome Co. for supplying bretylium tosylate (Darenthin, Bretylate).

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Circulation. 1972;45:1024-1034
doi: 10.1161/01.CIR.45.5.1024

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