Evaluation of Bretylium Tosylate for the Treatment of Premature Ventricular Contractions

By DONALD W. ROMHILT, M.D., SAUL S. BLOOMFIELD, M.D., RAYMOND J. LIPICKY, M.D., RICHARD M. WELCH, PH.D., and NOBLE O. FOWLER, M.D.

SUMMARY
In a controlled setting bretylium tosylate was evaluated for efficacy, toxicity, onset, and duration of action in eight patients with frequent premature ventricular contractions (PVC). Four patients received a single im dose of bretylium, 4 mg/kg, with before and after control days; the other four patients received bretylium, 2 and 4 mg/kg, on different days with before and between control days. PVC were quantified from stored continuous ECG tape recordings by an automated arrhythmia-detection system. Five patients had 50% or more reduction of PVC frequency with bretylium 4 mg/kg, and one with 2 mg/kg. Bretylium 4 mg/kg but not 2 mg/kg reduced mean PVC frequency by half beginning at the sixth hour and continuing for 12 hours. Hypotension began within 1 hour. Maximum fall in mean supine blood pressure was 17/6 mm Hg with 2 mg/kg, and 25/12 mm Hg with 4 mg/kg. Plasma bretylium concentration was maximum at about 1 hour with a mean elimination half-life of 10 hours. A controlled quantitative method for evaluation of antiarrhythmic drugs in man demonstrated that bretylium can be effective in suppressing PVC frequency. The dissociation between hypotensive and antiarrhythmic effects of bretylium suggested that its antiarrhythmic effect was independent of adrenergic neuronal blockade.

Additional Indexing Words:
Antiarrhythmic drug  Continuous ECG monitoring  Arrhythmia quantification  Automated arrhythmia detection

In 1966 BACANER reported that bretylium tosylate, an adrenergic neuronal blocking drug, markedly increased the ventricular fibrillatory threshold in dogs. Subsequently it was reported that bretylium was effective in the treatment of acutely ill patients with refractory ventricular arrhythmias. These studies were uncontrolled, and there was sometimes a delay as long as 7 hours in the onset of drug effect. Aravindakshan, Gettes, and Surawicz questioned the value of bretylium in patients with refractory arrhythmias, and others have demonstrated the lack of efficacy of bretylium in ventricular arrhythmias secondary to digitalis toxicity in dogs. Also, there have been conflicting reports on the efficacy of prophylactic bretylium in the suppression of ventricular arrhythmias after acute myocardial infarction. In a controlled study it was reported that prophylactic bretylium was of no value in preventing ventricular arrhythmias following acute myocardial infarction but was effective for the...
suppression of supraventricular arrhythmias, while in an uncontrolled study by bretylium was found to be effective in both treatment and prevention of ventricular arrhythmias after acute myocardial infarction. It has been reported that bretylium given prophylactically decreased the incidence of postoperative ventricular arrhythmias following prosthetic valve replacement.

The purpose of this study was to evaluate bretylium in a controlled setting in patients with premature ventricular contractions (PVC) with precise quantification of PVC frequency, frequent arterial pressure and heart rate measurements, and serial plasma determinations of bretylium. This evaluation of efficacy and toxicity with two different dosages was also intended to define bretylium's onset and duration of action and to relate plasma levels to antiarrhythmic activity and hypotensive effects.

**Methods**

Patients were selected for study when the following criteria were fulfilled: PVC were present at a frequency of at least 1–2/min on routine electrocardiograms (ECG) for 2–3 days prior to entry into study. Patients were not receiving other known antiarrhythmic agents. The PVC were considered not to be secondary to digitalis toxicity, and patients did not have congestive heart failure requiring digitalization. The clinical condition of the patients was stable, and they were not in a life-threatening situation (absence of acute myocardial infarction or electrolyte imbalance).

Eight patients, whose characteristics are presented in table 1 (three patients were clinically refractory to therapy with recognized antiarrhythmic agents), were studied in two coronary care units at the University of Cincinnati Medical Center. Each patient served as his own control. The first four patients, who were studied for 3 days, received a single intramuscular dose of bretylium 4 mg/kg after a 24-hour control day. An additional 24-hour control day followed the bretylium-treatment day. The second four patients were studied for 4 days and received a single intramuscular dose of bretylium 2 mg/kg on the second day, and of 4 mg/kg on the fourth day with control days before each treatment day. Each control day began with an intramuscular injection of saline placebo. All doses of bretylium and saline were given under single-blind conditions. Patients were kept supine for at least 12 hours following bretylium or saline administration.

Identification and quantification of all PVC, including single ectopic beats, were achieved with instrumentation that combined a 72-hour tape recorder with an automated ectopic-beat detector. Continuous ECGs were recorded for the entire study period with an Avionics tape recorder attached to the bedside monitor. The stored ECG tapes were then played back at real time and processed through a Hewlett-Packard automated arrhythmia-detection system. This system recognized PVC by two criteria: (1) change in R-R interval by more than 20%, and (2) widening of the QRS by more than 0.015 sec, as compared with the average of four normal QRS complexes for that patient. The instrument was set to print out an intermittent ECG which contained a complete record of all PVC fulfilling either of these two criteria. The time of each PVC to the nearest minute was recorded on the ECG by an automatic time stamp. A nurse-technician

<table>
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<td><strong>Patient Characteristics</strong></td>
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<td>7*</td>
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<td>8</td>
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*Refractory to other antiarrhythmic agents.
observed the system during the entire period of data processing to assure accuracy. ECG printouts were read by the investigators, and all PVC were identified and quantified on an hour-by-hour basis. From this analysis the efficacy, onset, and duration of antiarrhythmic action of bretylium were measured.

After bretylium administration, arterial pressure and apical heart rate were obtained at 5-min intervals for the first hour, 15-min intervals for the next hour, 30-min intervals for the next 4 hours, and then at 1-hour intervals. Plasma concentrations of bretylium were measured by gas chromatography\textsuperscript{11} at the following hours after administration of the drug: 0, \( \frac{1}{3}, 1\frac{1}{3}, 3, 6, 12, \) and 24. Vanillylmandelic acid (VMA), epinephrine, norepinephrine, and bretylium excretion were determined from urine collected in two consecutive 3-hour aliquots after saline and bretylium administrations.

**Results**

**Antiarrhythmic Response to Bretylium Treatment**

Of the eight patients who received bretylium 4 mg/kg, five had at least a 50\% decrease in PVC frequency, one patient (no. 8) had less than 50\% reduction, and two patients (no. 2 and 6) had no discernable response. Only one (no. 5) of the four patients receiving the 2-mg/kg dose had a 50\% reduction in PVC frequency (table 2). In addition, two of three patients, who had been clinically refractory to other antiarrhythmic agents before study, had a 50\% reduction of PVC frequency with the 4-mg/kg dose of bretylium. Examples of bretylium effect in four patients are shown in figure 1. Although patients 1, 3, and 4 had a 50\% or greater response to treatment, the onset and duration of effect was variable.

By averaging data for all patients during each day of the study, the time-effect relationship of PVC frequency during treatment days was compared with that observed during control days (fig. 2). On day 2, the 2-mg/kg dose of bretylium was not associated with any appreciable change in the mean number of PVC per hour as compared with control values recorded on days 1 and 3. By contrast, the administration of 4 mg/kg of bretylium was associated with a 50\% reduction in mean PVC per hour during part of day 4 as compared with control values recorded on day 3 and after day 4. However, the onset of suppression of mean frequency of PVC with 4 mg/kg was delayed. As shown in figure 3, a 50\% reduction in mean PVC frequency was not seen until the sixth hour after administration. It was noted also that antiarrhythmic effect reached a peak at about the ninth hour after administration and persisted for about 12 hours. However, there were considerable individual differences in the onset of antiarrhythmic action, which ranged from the first to the ninth hour, and in the duration of this effect, which varied between 8 and 26 hours. In one patient (no. 5) who responded to both the 2-mg/kg and 4-mg/kg doses, the time of onset and magnitude of the decrease in PVC frequency were similar with the different dosages, but with the higher dose of bretylium the duration of action was more than twice as long.

**Hypotensive Effect of Bretylium**

Hypotension was the only side effect of bretylium that was observed. Each of the

<table>
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<th>Pt no.</th>
<th>Decrease in PVC frequency (%)</th>
<th>Peak plasma conc (mg/ml), at:</th>
<th>Plasma half-life (hr), at:</th>
</tr>
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<tr>
<td></td>
<td>2 mg/kg</td>
<td>4 mg/kg</td>
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<td>&lt;50</td>
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eight patients had a fall in supine arterial pressure with the 4-mg/kg dose, and three of four with 2 mg/kg (fig. 4). Three patients (no. 5-7), of whom one (no. 5) had a reduction of PVC frequency with 2 mg/kg, had an initial rise in arterial pressure in the first 5-10 min after the 2-mg/kg dose followed by a fall during the next 10-20 min in two of the patients (no. 5 and 7). With 4 mg/kg no initial rise in arterial pressure was observed. Two patients (no. 1 and 8) had marked hypotension with 4 mg/kg of bretylium but were asymptomatic and did not have clinical signs of shock. The maximum fall in the supine mean systolic and diastolic arterial pressures for all patients was 17/6 mm Hg with the 2-mg/kg dosage and 25/12 mm Hg with the 4-mg/kg dosage. There was wide individual variation in the maximum fall in supine arterial pressure with the 4-mg/kg dose ranging from 6/2 to 66/36 mm Hg.

In contrast with the antiarrhythmic response, there was no delay in the onset of the hypotensive effect with bretylium. The fall in mean systolic and diastolic arterial pressures was present within 20-30 min of administration. Hypotension reached its lowest point at the fourth hour on the average and lasted until the ninth hour with the 4-mg/kg dose (fig. 3).

Every patient had a fall in arterial pressure with the 4-mg/kg dose, yet only five patients had a clear reduction in PVC frequency. Patients (no. 1 and 8) with the greatest fall in arterial pressure did not have the largest reduction in frequency of PVC, and patients (no. 3 and 5) with the greatest reduction in PVC frequency had only a moderate fall in arterial pressure. Therefore, it was impossible to predict which patients would have an antiarrhythmic response on the basis of their hypotensive reaction.

Changes in apical heart rate at the time of maximum fall in arterial pressure were found to be inconsistent (fig. 4). With 4 mg/kg of bretylium, five of eight patients had a
Figure 2
Mean PVC frequency during treatment days compared with control days. There was 50% suppression of mean PVC frequency in the second and third 6-hour intervals following bretylium 4 mg/kg (solid bars), while no suppression was seen after 2 mg/kg (shaded bars). Control days are shown in stippled bars. N refers to number of patients. On day 1, data were not obtained in one patient during the first 12 hours due to recording-equipment failure.

Plasma Levels of Bretylium
The time course of appearance and disappearance of bretylium in the blood (mean plasma levels for eight patients), following intramuscular administration of 4 mg/kg, is shown in figure 3. The course is consistent with the usual concept of absorption (primarily influencing the earliest portion of the curve), absorption and distribution (primarily influencing the middle portion), and elimination (primarily influencing the terminal portion). Least-square fits to the terminal portion (6-, 12-, and 24-hour samples) of each patient’s results gave the elimination half-lives listed in table 2. The mean \((\pm SEM)\) elimination half-life was 9.76 \((\pm 1.48)\) and 11.89 \((\pm 2.47)\) hours with the 4- and 2-mg/kg doses, respectively. There was wide individual variation, the range being between 4.2 and 16.9 hours. The long elimination half-life is consistent with our finding that only 10% of unchanged bretylium was excreted in the urine in the first 6 hours after administration.

Peak plasma concentration of bretylium with the 4-mg/kg dose was in a range...
BRETYLIUM TOSYLATE FOR PVC

between 670 and 1500 ng/ml, and with the 2-mg/kg dose between 500 and 650 ng/ml (table 2). The mean plasma concentration of bretylium was found to be maximum between ½ and 1½ hours after intramuscular administration (fig. 3). At 1½ hours after administration the mean plasma concentration was 502 ng/ml with the 2-mg/kg dose, and 971 ng/ml with the 4-mg/kg dose.

Relationship of Antiarrhythmic and Hypotensive Effects to Plasma Bretylium Levels

An association was observed between the early onset of hypotensive effect and the time of peak plasma bretylium concentration, but the onset of antiarrhythmic activity was delayed until the sixth hour when mean plasma level had declined to less than one half of the highest value (fig. 3). Maximum mean plasma concentration of bretylium occurred at about 1 hour after administration and coincided in time with the onset of hypotension. By contrast, the onset of antiarrhythmic effect at the sixth hour after administration coincided with the beginning of the terminal phase of the decline curve for plasma bretylium, i.e., about 5 hours after peak levels had been reached. Since the antiarrhythmic effect was prolonged, it may have been related to the plasma half-life of bretylium during the terminal phase, which also tended to be relatively long. This is suggested by the finding that of three patients with the longest half-lives, two (no. 3 and 5) had a prolonged antiarrhythmic response with the 4-mg/kg dose, 22 and 17 hours, respectively.

Urinary VMA, epinephrine, and norepinephrine levels on the average were either unchanged or reduced after administration of 2 or 4 mg/kg of bretylium.

Discussion

This study describes a controlled quantitative method for therapeutic evaluation of antiarrhythmic drugs in man. With this precise method, a drug can be carefully evaluated in a controlled setting for antiarrhythmic efficacy relative to adverse effects and plasma concentration.

Our data suggest that bretylium is of therapeutic value in the treatment of patients with PVC, but its usefulness clinically may be limited by some of its undesirable properties. First the onset of antiarrhythmic effect after intramuscular administration was quite variable with an average delay of about 6 hours. This may account in part for earlier conflicting reports

Figure 3

Comparison of the onset and duration of action of bretylium, 4 mg/kg, on PVC frequency and arterial pressure in relation to blood levels. On the average, hypotensive effect was present in the first hour, when mean plasma concentration of bretylium was at its peak, and continued until the ninth hour after administration. By contrast 50% suppression of mean PVC frequency began at the sixth hour and continued until the 18th hour. The mean elimination half-life of bretylium was about 10 hours. N refers to number of patients.

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it were not for the marked hypotension, which was found in some patients, bretylium might be more useful as an antiarrhythmic agent. The significant fall in supine arterial pressure found in the present study was not reported in one earlier study, but was observed in another. In the latter study, the administration of bretylium was discontinued because of hypotension in one third of patients receiving it prophylactically after an acute myocardial infarction. It was suggested in the former study that larger doses of bretylium (5-10 mg/kg) might overcome supine hypotension because of bretylium’s alleged positive inotropic effect. However, in the present study it was found that the mean fall in supine arterial pressure with a 4-mg/kg dose was greater than with 2 mg/kg. No other side effects of bretylium were observed in the present study. In particular, nausea and vomiting which at times have been associated with the intravenous route of administration did not occur with the intramuscular route.

One of the advantages of bretylium was its efficacy in some patients who were refractory to other commonly used antiarrhythmic agents. An additional benefit of bretylium was the prolonged duration of action which might render it useful in continued maintenance therapy for suppression of recurrent ventricular arrhythmias. Furthermore, as previously alluded, bretylium has been reported to have the very desirable distinction of being the only antiarrhythmic agent with a positive inotropic effect. The exact mechanism of bretylium’s antiarrhythmic action has not been determined. It has been reported that bretylium differs from all other antiarrhythmic agents in that it does not decrease automaticity, nor depress phase-four depolarization, and bretylium fails to lengthen the effective refractory period in relation to action potential duration, even though it prolongs both variables individually. Therefore, it has been suggested that bretylium’s antiarrhythmic action is related to

Figure 4
Maximum change in supine arterial pressure with concomitant changes in heart rate in individual patients. With bretylium, 2 mg/kg, there was an initial rise in arterial pressure in three of four patients followed by a decrease in two. With 4 mg/kg, all eight patients showed only a decrease in supine arterial pressure. Patients 1 and 8 had marked hypotension. S refers to systolic and D to diastolic.
depletion of catecholamines from adrenergic nerve terminals.

In the present study, however, it was found that there was a dose-dependent and a temporal dissociation between the antiarrhythmic and hypotensive effects of bretylium. The higher dose of bretylium produced both hypotensive and antiarrhythmic effects whereas the lower dose, while retaining hypotensive effect, was virtually devoid of antiarrhythmic efficacy. Furthermore, the delay in the onset of the antiarrhythmic effect with the 4-mg/kg dose was in contrast with the early onset of the hypotensive effect. It seems significant that the onset of antiarrhythmic activity occurred well after peak plasma level of bretylium had been reached, while hypotension began at a time when plasma levels were still increasing. It suggests that after uptake into sympathetic nerves, bretylium may need to be distributed to another compartment before the appearance of antiarrhythmic activity.

These findings provide indirect evidence that the antiarrhythmic effect of bretylium is independent of its adrenergic neuronal blocking action, and are in agreement with the report that bretylium's capacity to elevate the fibrillatory threshold in dogs was not abolished by chronic denervation and reserpine treatment.

Acknowledgments

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