Experience with Bretylium Tosylate
By a Hospital Cardiac Arrest Team

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SUMMARY The effect of bretylium tosylate (BT) was determined in 27 consecutive cases of resistant ventricular fibrillation (VF) encountered by a hospital cardiac arrest team. The VF was sustained and completely resistant to multiple injections of lidocaine, sequential DC shocks at 400 watt-sec and one or a combination of intravenous propranolol, diphenhydantoin or procainamide. Following 30 min of sustained cardiac massage, BT (5 mg/kg i.v.) was administered. In 20 patients, VF was terminated within 9–12 min after DC shock. Eight of these patients failed to recover while 12 (44%) of all patients resuscitated survived to be discharged from hospital. Eleven out of 20 (55%) of all patients who had a cardiac arrest outside the CCU were survivors; only one out of seven in the CCU was successfully resuscitated. While receiving maintenance BT post-resuscitation (5 mg/kg i.m. q 6–12 hrs x 48 hrs), half the patients developed hypotension and three required vasopressors and/or fluid replacement.

The data indicate that BT is a useful agent in patients with sustained VF refractory to repeated lidocaine injections, some other antiarrhythmic agents, and multiple DC shocks.

THE WIDESPREAD USE OF ANTIARRHYTHMIC AGENTS in coronary care units has succeeded in decreasing the incidence of ventricular fibrillation (VF) as a primary electrical disorder.1 It is estimated, however, that 30–50% of in-hospital deaths from ischemic heart disease occur suddenly either during the postcoronary care unit phase or on arrival in the emergency room.2 A rapid effective in-hospital mobile cardiac arrest team can serve as an extended CCU for these patients, and in fact, our experience since 1962 revealed that a significantly higher survival rate from resuscitation, presumably after primary VF developed, occurred in patients arresting outside the CCU compared to those within. A decade’s experience from our hospital4 also revealed that an increased survival rate from resuscitation occurred suddenly in 1966–67 and was sustained thereafter. This was the period during which lidocaine was introduced as a routine antiarrhythmic agent in resuscitative measures for resistant VF. Although a causal relationship between the use of lidocaine and the increased survival rate cannot be established with certainty, it raises the tantalizing suggestion that cases of primary VF that remain resistant to lidocaine therapy may respond to a different antiarrhythmic agent.

Since 1966, a number of clinical studies have demonstrated that bretylium tosylate is an effective drug against recurrent ventricular arrhythmias complicating myocardial infarction.6 The aim of this study was to evaluate the efficacy of bretylium tosylate on VF resistant to multiple DC shocks, lidocaine, and a variety of antiarrhythmic agents.

Methods

The Royal Victoria Hospital is a 1,100 bed University Teaching Hospital where an average of 154 calls for cardiac arrests are handled by a single mobile resuscitation team each year. This study deals with the period from July 1970 to January 1973 where out of a total of 330 cardiac arrests, 27 consecutive cases were encountered in whom VF was sustained and completely resistant to the conventional forms of electrical and pharmacological resuscitative therapy over a 30-minute period. These 27 cases form the basis of this report. Twenty-one of these patients had ischemic heart disease, two patients were recovering from aortic valve replacement, and one each had subacute bacterial endocarditis, renal failure, digitalis toxicity, and trauma.

The composition and operation of the mobile cardiac arrest team has been described in a previous report.9 Briefly, the four-member team was gathered in the CCU and consisted of a senior and junior house officer attached to the acute care cardiorespiratory service, a specially trained nurse and an inhalation therapist. All cardiac resuscitations in hospital were carried out by this team, and following initial recovery, the same team continued to care for the patient in the CCU. Seven resuscitations were performed within the CCU and 20 occurred in other areas of the hospital including the medical and surgical wards, emergency room, and postoperative recovery areas.

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A cardiac arrest was defined as a sudden circulatory collapse characterized by pulselessness, apnea, unconsciousness, and a rhythm disturbance incompatible with effective cardiac contraction. The first arrhythmia detected in all patients in this study was VF. The experimental protocol was designed as follows. The general principles of appropriate resuscitation techniques were adhered to in each case including external cardiac massage and early endotracheal intubation. Assisted ventilation was applied using oxygen-enriched mixtures and careful attention to acid-base balance was reflected in frequent arterial blood gas determinations and appropriate titration with intravenous sodium bicarbonate. During the first 10 min, all patients received at least two bolus injections of 100 mg of lidocaine followed by an infusion rate of 50 μg/kg/min. At least one electrical DC countershock of 400 watt-sec was applied to the precordium before and every 3–5 min following lidocaine administration. During the second 10 min interval the above procedures were repeated and the following adjunctive measures were tried. Every case received an intravenous bolus of at least one or a combination of the following agents: procainamide (0.1–0.5 g i.v.), 16 cases; propranolol (2–5 mg i.v.), 10 cases; and diphenhydantoin (250 mg i.v.), 7 cases. As required, an attempt to sensitize the fibrillatory pattern to inotropic agents was made by injecting either intravenous calcium chloride (10 ml of 10% solution) or intracardiac injection of epinephrine HCl (1–2 cc of 1:10,000 solution).

Following 20–30 min of sustained external cardiac massage and employment of all the above measures, VF persisted in all patients. At no time during the period of resuscitation was there any evidence of spontaneous or post DC shock rhythm change from VF. As a final measure, a single intravenous bolus of bretylium tosylate* (5 mg/kg) was administered. Standard resuscitation techniques continued for another 15–20 min following the bretylium injection. In those patients who survived initial resuscitation, bretylium tosylate was prescribed for maintenance therapy (5 mg/kg) intramuscularly every 6–8 hours for 48 hours.

The results were analyzed in terms of the initial response to bretylium, the time delay for this response and ultimate survival. The latter term was defined as patients who not only recovered from initial resuscitation but were eventually discharged from the hospital.

Results

In 20 out of the 27 patients (74%), bretylium facilitated successful electrical cardioversion of VF to some form of stable rhythm pattern for the first time in 30 min of continuing VF (table 1). Twelve out of 27 patients (44%) survived to leave hospital as a result of bretylium tosylate. The drug had no effect on seven patients and in the eight nonsurvivors in whom VF was terminated, there was complete electromechanical dissociation presumably as a result of pump failure. None of these patients survived the resuscitation. Among the 20 patients whose arrhythmia was reverted, usually one and rarely more than two DC shocks were necessary subsequent to the bretylium injection. The time to reversion averaged 9.2 min for the survivors and 11.5 min in the nonsurvivors. These were not statistically significant. The administration of antiarrhythmic drugs other than lidocaine did not influence the outcome as these agents were evenly distributed among both survivors and nonsurvivors. Ten of 22 patients, or almost one-half of those with ischemic heart disease, were successfully resuscitated with bretylium.

Although the members of the cardiac arrest team and the crash cart are located in the CCU, there was only one survivor out of the seven patients in the CCU who had resistant VF (fig. 1). Virtually all patients with acute myocardial infarction who had ventricular arrhythmias were on lidocaine therapy in our CCU and, therefore, it is presumed that the poor survivor rate in the unit was due to the high incidence of pump failure and cardiogenic shock. Eleven out of 20, or more than 50%, of those patients who developed VF on the wards and emergency room survived.

All 12 surviving patients received maintenance bretylium therapy in the form of i.m. injections (5 mg/kg) every 6–8 hours for 48 hours. In figure 2 the highest values for systolic blood pressure were defined as those occurring within the first 12 hours following recovery from resuscitation. Despite an average value of 122 mm Hg and a rather narrow range during the early postresuscitation period, 9 of 12 patients showed moderate hypotension during maintenance bretylium therapy. Six of the patients reached values of 90 mm Hg or less and in three of these patients treatment with fluid replacement and/or vasopressor therapy was instituted.

Discussion

A number of uncontrolled studies have shown bretylium to be effective against refractory ventricular tachyarrhythmias and recurrent ventricular fibrillation complicating myocardial infarction. To the best of our knowledge, this is the first report demonstrating the ability of bretylium to facilitate successful cardioversion for those patients with primary ventricular fibrillation which is sustained and resistant to standard resuscitative procedures and a variety of

*Bretylium. Kindly supplied by Burroughs-Wellcome Laboratories in Montreal, Quebec, Canada.

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**Figure 1.** Geographic distribution of resuscitations. Percentages in brackets refer to percentage of all resuscitations which occurred at that site. E.R. = emergency room; S = survivors of resuscitation; N.S. = nonsurvivors.
antiarrhythmic drugs. This study indicates therefore that certain patients who develop sudden cardiac arrest in hospital have sustained and resistant primary ventricular fibrillation which is responsive to bretylium tosylate.

As a pharmacological experiment, this study suffers from obvious unsteady state conditions and the previously administered antiarrhythmic agents which could conceivably have exerted a delayed effect. Nonetheless, there appeared to be a direct temporal relationship between the administration of bretylium and time of reversion (9–12 min). This time interval is in keeping with the known onset of the drug's action in the presence of other antiarrhythmic agents.\(^5\)\(^,\)\(^7\)

Taylor et al. used bretylium in a controlled trial to evaluate its efficacy as a prophylactic agent in acute myocardial infarction.\(^11\) They found no significant decrease in the incidence of ventricular dysrhythmias and a 30% incidence of troublesome hypotensive episodes requiring withdrawal of the drug. The failure of bretylium to prevent ventricular ectopic activity as opposed to its effect on refractory VF may arise from its electrophysiologic properties. The drug's ability to raise the ventricular fibrillation threshold has been documented\(^12\) although the mechanism is not fully understood. The raised threshold may be related to the drug's hyperpolarizing effect by virtue of an early transient release of norepinephrine from adrenergic nerve terminals.\(^9\)\(^,\)\(^14\) More recent studies indicate that bretylium can prolong the action potential duration along the entire proximal conducting system while reducing the prolonged duration in cells from acutely infarcted regions.\(^16\) This uniform lengthening of refractoriness and hyperpolarization would favor a state of electrical uniformity throughout the tissue, thereby reducing the opportunity for reentrant circuits to develop.

A 20% decrease in systolic blood pressure occurred in three-quarters of the survivors while on 48 hour maintenance bretylium. While other factors may have contributed to the variations in systolic pressures following at least 30 min of cardiopulmonary resuscitation, the fact that all nine patients with hypotension demonstrated an improvement in blood pressure on discontinuation of bretylium implies that the drug was partly responsible for the hypotensive state during the 48 hour postresuscitation period. In only three of the 12 survivors were vasopressor agents and/or fluid replacement thought necessary to control the blood pressure during maintenance therapy. We do not feel that hypotension is a serious enough side effect to preclude the use of maintenance bretylium following resuscitation. Although this study does not indicate whether maintenance therapy is indeed necessary, several patients demonstrated short salvos of ventricular ectopic beats when the interval between the injections was prolonged from eight to 12 hours. One patient could not be weaned from bretylium at any time during his 5 week hospital course without developing serious and malignant ventricular ectopic activity. He was subsequently discharged on oral bretylium (Darenthin) 200 mg t.i.d.

Recent reports suggest that bretylium may increase infarct size as a result of its inotropic properties.\(^16\) There is no clinical evidence to date which substantiates this theory and the animal experiments attesting to the drug's effect on increased infarct size must be weighed against those experiments showing augmented coronary flow and possible inhibition of coronary vascular spasm.\(^17\) These hemodynamic properties should in no way detract from its effect as an antiarrhythmic agent for resistant ventricular fibrillation. Until such time as its clinical effect in ischemic heart disease becomes firmly established, it would probably be best to confine its use to resistant and/or malignant ventricular arrhythmias.

The geographic distribution of hospitalized patients suffering sudden cardiac arrest with resistant VF coincides with the observed distribution of cardiac arrests in general.\(^5\)\(^,\)\(^7\) Primary electrical disorders, therefore, still occur in hospital and this study indicates that following the failure

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**Table 1. Effect of Bretylium Tosylate on Resistant Ventricular Fibrillation**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Age (mean)</th>
<th>Successful Reversion</th>
<th>Time to Reversion (min)*</th>
<th>Coronary Disease</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors</td>
<td>12</td>
<td>61</td>
<td>12</td>
<td>9.2 ± 3.5</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>15</td>
<td>59</td>
<td>8</td>
<td>11.5 ± 5.2</td>
<td>11</td>
<td>4</td>
</tr>
</tbody>
</table>

Survivors are defined as those patients who, following successful resuscitation, were ultimately discharged from hospital. Successful reversion means conversion of VF by electroshock to some form of stable electrical rhythm.

*Mean ± standard error of the mean.

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**Figure 2.** The maximum change in systolic blood pressure during the 48 hour postresuscitation period while on maintenance bretylium therapy. Highest refers to the highest systolic pressure recorded during first 12 hours following recovery from resuscitation. Lowest refers to the lowest recorded pressure thereafter. The closed dots with vertical bars are the mean and standard error of the mean.
of conventional resuscitative efforts, many of these patients can be saved with the administration of intravenous bretylium tosylate. This is not to say that bretylium tosylate is either superior or should be used in preference to other antiarrhythmic agents. As Koch-Weser has indicated, it may very well be that equal numbers of patients unresponsive to bretylium may derive a similar benefit from lidocaine if the sequence of the antiarrhythmic agents were reversed. This thesis however, has not been proven and, judging from this series of patients, would merit careful scrutiny and further clinical testing.

References
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