Life threatening ventricular dysrhythmias: Intervention with bretylium tosylate

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Cardiac arrhythmias following acute myocardial infarction are often fatal. Although commonly used antiarrhythmics are usually effective, some patients develop dysrhythmias that are refractory to these medications. This article discusses the use and contraindications of bretylium tosylate, a relatively new antiarrhythmic drug that has been shown to be effective in reversing dysrhythmias that were refractory to other drugs.

Mortality rates of patients with acute myocardial infarction (AMI) remain very high. Current statistics show that at least 50% of all patients with AMI never reach the hospital. Of the remaining half who do enter medical facilities, 15% die during hospitalization. Lethal cardiac dysrhythmias resulting from myocardial ischemia still constitute the most frequently seen complication of AMI.

Interestingly, continuous monitoring during early phases of infarction has shown that about 40% of patients who develop ventricular fibrillation experience no significant warning arrhythmias. Such findings make a strong case for the administration of prophylactic antiarrhythmic therapy. Currently, most institutions routinely use lidocaine as a preventive measure in all suspected and documented AMIs.

The commonly used modes of drug therapy designed to inhibit cardiac irritability are very effective. Yet some patients continue to exhibit life-threatening dysrhythmias refractory to routine medications. New antiarrhythmic drugs that can be safely used in the clinical setting are constantly being researched and evaluated.

The intent of this paper is to explore bretylium tosylate (Bretylol\textsuperscript{	extregistered}), an antiarrhythmic which is new in the sense that its approval for use in this country is recent. Because of the acute setting in which parenteral antiarrhythmics are given, it is of the utmost importance that CRNAs be totally familiar with all aspects of any antiarrhythmic drug's actions.

To familiarize the reader with the actions, administration and implications of bretylium tosylate, this article will discuss the electrophysiologic events and their interplay with systematic reactions that induce and aggravate cardiac arrhythmias.

Arrhythmogenesis

Although the exact mechanisms and sites of ventricular dysrhythmias are unknown, arrhythmias following AMI occur as a result of cellular ischemia and necrosis from coronary arterial occlusion. Two general factors likely to contribute to the development of dysrhythmias are: (1) changes in cellular electrophysiology of the myocardium; and (2) geometric changes of the musculature (that is, infarct size and location).\textsuperscript{1}

Electrophysiologic changes. Ventricular muscle cells are completely dependent upon coronary
blood flow for substrates and oxygen. Thus arterial occlusion has an immediate profound effect on cellular metabolism. Hypoxia leads to a decrease in high-energy phosphate bond production and a lowering of available adenosine triphosphate (ATP). Diminished ATP stores within the ischemic cells inhibit their capacity to actively extrude sodium and transport potassium inwardly. As a result, sodium accumulates intracellularly and potassium is lost to the extracellular space.

The influx of calcium ions into the cell is similarly reduced, adding to the impairment of actinomyosin coupling within the muscle tissue. Anaerobic metabolism ensues, leading to a build-up of lactic acid, which leaks into the extracellular space and lowers the pH. Other noxious metabolites from anaerobic processes set the stage for electrophysiologic alterations in the ischemic cell.

**Hemodynamic effects.** The efficiency of the cardiovascular system is dependent upon the interplay of intrinsic and extrinsic regulatory mechanisms. Intrinsic factors include ventricular end-diastolic filling pressure (preload) and ventricular inhibition of ejection (afterload). Extrinsically, the autonomic nervous system attempts to preserve cardiovascular homeostasis by vascular tone manipulations which maintain flow to vital organs and adequate cardiac output (Figure 1).

The systemic hemodynamic effects of lethal dysrhythmias are profound. Unrelieved ventricular tachycardia and ventricular fibrillation, by nature of their high rates and low stroke volume, bring cardiac output levels to near zero. Consequently, any defense by the autonomic nervous system via feedback mechanisms becomes useless, and death rapidly follows.

**Antiarrhythmic drug therapy**

The clinical use of antiarrhythmics is based almost entirely on empirical knowledge because of lack of understanding of the molecular basis of antiarrhythmic agents and of the exact mechanisms of their actions. Researchers are stymied by the experimental difficulties posed by the peculiar structural and functional properties of myocardial conductive and muscular tissue.

The effects of antiarrhythmic drugs involve a complex interplay between direct cellular membrane actions and changes in autonomic tone. Various regions of the heart respond differently to medications. For example, lidocaine depresses automaticity of the Purkinje fibers and shortens the refractory period and action potential. Procainamide lengthens the refractory period and depresses excitability by raising the ventricular fibrillation threshold. Adding to the complexity of drug actions are the differing responses to treatment between normal, hypoxic and necrotic cells.

Bretylium was originally introduced in the 1950s as an antihypertensive agent. Because of undesirable effects such as postural hypotension and poor and inconsistent absorption, the drug never came into full usage. In 1965, Leveque first reported its antiarrhythmic properties in dogs. Structurally, bretylium is one of a series of quaternary ammonium compounds; whether its antiarrhythmic effects are due to the ammonium structure is uncertain at present.

Bretylium is taken up at the adrenergic nerve terminals of the sympathetic nervous system—particularly cardiac sites—where it prevents release of norepinephrine during sympathetic firing. Bretylium's initial neuronal effect on administration is paradoxical; norepinephrine is released from nerve fibers and thus the drug has a sympathomimetic effect. This action accounts for the observed transient increase in arterial blood pressure, heart rate, and peripheral vascular resistance, as well as

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for aggravation of existing arrhythmias. Fortunately
this sympathomimetic effect subsides within 20-30
minutes.14

Following the sympathomimetic phase, bretylium inhibits further release of norepinephrine from the peripheral nerve terminals. This type of neuronal blockage takes only a few minutes to reach peak effect. It must be emphasized that bretylium does not depress sympathetic nerve conduction, but merely prevents norepinephrine release when the nerve terminal is depolarized. Because centrally mediated (adrenal medulla) sympathetic firing is not affected by moderate dosages of bretylium, norepinephrine release in sympathetic nerves elsewhere in the body is not inhibited.7

A positive inotropic effect not found in other antiarrhythmics has been noted with bretylium administration. This phenomenon could be due to the initial sympathomimetic effect or to a direct membrane action as yet not understood.

Microelectric studies have shown that therapeutic (0.6 to 20 mg/ml) concentrations of bretylium consistently increased the action potential duration and length of effective refractory period in ventricular muscle cells and Purkinje fibers (Table I). Other antiarrhythmics, including lidocaine, procainamide, and quinidine, depress Purkinje fiber automaticity; bretylium does not. In addition, bretylium does not alter the normally occurring ratio between action potential and effective refractory period as do most other drugs. Most importantly, bretylium's power to prolong action potential and refractory period without slowing conduction causes the wave length of re-entrant pathways to be altered, thereby decreasing susceptibility to lethal arrhythmias.12

Canine studies have revealed that after administration, the initial positive inotropic effect wore off within 45 minutes. Following that point there was no difference in preload, aortic pressures, or ejection fraction between the bretylium-treated dogs and the control group.18

Human studies have exhibited profound hemodynamic effects with bretylium. Chatterjee and associates administered bretylium intravenously to seven patients, five of whom were normotensive and two of whom were mildly hypotensive.2 Control levels of bretylium returned within 15 minutes after initial norepinephrine discharge. However, within two hours, heart rate, blood pressure, and peripheral vascular resistance all dropped significantly.

By examining findings such as these, it would seem likely that bretylium may somewhat enhance left ventricular performance by reducing the afterload. However, the potential for marked hypotension probably cancels any positive effects on ventricular performance.

Hypotension clearly is the most deleterious systemic effect encountered with bretylium usage. It occurs because the inhibition of norepinephrine release keeps peripheral vascular resistance low. Fifty percent of patients treated with bretylium

| Table I |
| Effect of bretylium, lidocaine, and procainamide on electrophysiologic properties of Purkinje fibers and ventricular muscle |

<table>
<thead>
<tr>
<th></th>
<th>Bretylium</th>
<th>Lidocaine</th>
<th>Procainamide</th>
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<tbody>
<tr>
<td>Purkinje fiber</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Automaticity</td>
<td>No change, increase*</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Membrane responsiveness</td>
<td>No change</td>
<td>No change, decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Action potential duration (APD)</td>
<td>Greatly increased</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Effective refractory period (ERP)</td>
<td>Greatly increased</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>ERP/APD</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Ventricular muscle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APD</td>
<td>Increased</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>ERP</td>
<td>Increased</td>
<td>Decreased</td>
<td>Increased</td>
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</tbody>
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*Initial increase is secondary to release of norepinephrine.

have exhibited marked degrees of hypotension as well as subjective responses of lightheadedness and dizziness. Therefore, it is extremely important that ECG, blood pressure, and, if possible, pulmonary artery pressures, be continuously monitored while bretylium is being given.

**Clinical indications of bretylium tosylate**

Because of its potential to cause hypotension, bretylium has been used only when other safer antiarrhythmics have been unsuccessful. Generally, bretylium has been shown to be quite effective in reversing dysrhythmias that were refractory to other drugs.

As part of a hospital cardiac arrest team, Holder and associates in 1977 treated 27 consecutive patients having refractory ventricular tachycardia and ventricular fibrillation with bretylium. The patients had been first treated with lidocaine, procainamide, standard cardiopulmonary resuscitation, and defibrillation, none of which worked. After a single 5 mg/kg intravenous bolus of bretylium followed by electric counter-shock, a stable heart rhythm was restored in 20 of the 27 patients. Twelve of the 20 survived to be discharged from the hospital; nine of those patients developed hypotension and three required fluid and/or vasopressor therapy.

In 1979 at the Touro Infirmary, a group of 18 AMI patients having recurrent ventricular fibrillation were treated with bretylium when repeated counter-shock in combination with the administration of lidocaine and procainamide was ineffective. Ten of these patients survived and eight died; most in the latter group had anterior myocardial infarctions complicated by cardiogenic shock. In the ten surviving patients, bretylium was effective within 10 minutes of administration in eradicating ventricular tachycardia and ventricular fibrillation. While some ectopy persisted in those patients, virtually all had no new episodes of ventricular tachycardia or ventricular fibrillation.

The study found that bretylium was particularly effective in patients presenting some level of atrioventricular block, in which the use of lidocaine and procainamide is contraindicated. The major problem was the postural hypotension seen in all 18 patients. Surprisingly, there was no evidence of an early sympathomimetic effect upon administration.

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**Table II**

<table>
<thead>
<tr>
<th>Bretylium tosylate dosages</th>
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<tr>
<td><strong>Initial therapy</strong></td>
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<tr>
<td>Emergency IV (during CPR, etc.)</td>
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<tr>
<td>IV</td>
</tr>
<tr>
<td>IM</td>
</tr>
</tbody>
</table>

**Maintenance therapy**

| IM | 5-10 mg/kg | 5-10 mg/kg every 6-8 hours | 30 mg/kg per day | Undiluted |
| IV intermittent | 5-10 mg/kg | 5-10 mg/kg every 6-8 hours | 30 mg/kg per day | Dilute as for IV therapy above |
| constant | 5-10 mg/kg | 1-2 mg per minute | 30 mg/kg per day | Dilute in D5W or NS and adjust volume as needed |

*More rapid IV administration may cause nausea and vomiting.*

**Dosage and administration**

The initial recommended dose is a bolus of 5 mg/kg body weight of bretylium given intravenously over several minutes, diluted four parts of 5% dextrose in water or normal saline to one part bretylium (see Table II). If this is not successful, a 10 mg/kg IV bolus given over 15 minutes may be administered. This dosage may be repeated until a total of 30 mg/kg has been injected. Blood pressure must be carefully monitored during administration.

For maintenance therapy, a continuous IV infusion of 1-2 mg/minute is usually given. An alternative to this is intramuscular administration of 5-10 mg/kg bretylium every six hours. Peak effects on maintenance dosages are reached within two to three hours. The duration of the anti-arrhythmic effect extends from 8-20 hours.\(^4\)

**Metabolism**

In rats, radioactive-labelled bretylium was found to be bound in cardiac receptor sites of the sympathetic nerve terminals. Concentration in cardiac (beta) nerve endings was 30 times greater than concentration in plasma or skeletal muscle. The sarcolemma is an additional binding site within the myocardium.\(^10\)

Plasma half-life of bretylium is seven hours. 70-80% is excreted unchanged in the urine during the first 24 hours of administration. Because it is removed via renal filtration, excretion rates are diminished in patients with renal insufficiency; caution must be exercised in giving bretylium to patients having renal disease. Unfortunately no data is available as to toxic levels or upper limits of therapeutic doses.\(^4\)

**Side effects and warnings**

Certainly the most blatant and potentially dangerous side effect routinely encountered with bretylium administration is hypotension. The other most commonly reported side effects are aggravation of existing dysrhythmias and nausea and vomiting.\(^4\)

Bretylium is contraindicated in patients whose arrhythmias are suspected to be a result of digitalis toxicity. Administration in the face of high serum digitalis levels serves to intensify the dysrhythmias, at least in feline studies. No human correlates are available, and the mechanisms involved are as yet not understood.\(^4\)

Bretylium should not be given to patients with fixed cardiac output syndrome (aortic stenosis), idiopathic hypertrophic subaortic stenosis, or pulmonary hypertension. The decrease in peripheral vascular resistance associated with bretylium cannot be compensated for in such circumstances due to the body's inability to raise cardiac output sufficiently.

**Summary**

The impact of psychogenic and physical stressors has been shown to have a negative effect on cardiovascular homeostasis (Figure 2). As CRNAs, we have a responsibility to maintain the patient's equilibrium under the stress-provoking conditions of surgery.

Experience in coronary care units over the last 16 years has shown that the majority of patients who develop primary ventricular fibrillation during AMI can be rapidly resuscitated by prompt defibrillation. Only in a small number of patients does ventricular tachycardia or ventricular fibrillation become recurrent or resistant to treatment. It is in this small number that bretylium has proven itself to be a life-saving treatment.

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**Figure 2.**
Modification of Neil's hypertension-stress model

- cortisol
- aldosterone
- ADH
- sodium retention
- renin
- blood volume
- sodium retention
- angiotensin
- potentiates sympathetic nervous system
- vasoconstriction
- blood pressure and heart rate
- myocardial O\(_2\) consumption
- myocardial ischemia
- cardiac arrhythmias
- probability of ventricular fibrillation

REFERENCES


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