Bretylium, a Class III Antiarrhythmic, Returns to the Market

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Bretylium, with an extensive pharmacologic and medicinal history, was approved by the United States Food and Drug Administration in 1986 for "*short-term prevention and treatment of ventricular fibrillation (VF) and treatment of life-threatening ventricular arrhythmias and ventricular tachycardia (VT) unresponsive to adequate doses of a first-line antiarrhythmic agent, such as lidocaine*." The NDA sponsor withdrew bretylium from the market in 2011, largely due to unavailability of raw materials required for its production; prior to this, bretylium was removed from the 2000 ACLS Guidelines algorithm for VF/pulseless VT given the challenges obtaining raw materials for drug manufacture. Recently, bretylium has been reintroduced into the US market by a generic pharmaceutical company with the same indications as before. This article provides a history of the salient trials evaluating the efficacy and safety of bretylium and looks to the future as bretylium finds its place in the modern day management of ventricular arrhythmia. **(Am J Cardiol 2020;133:77−80)**

Bretylium has an extensive history in nonclinical pharmacology, clinical pharmacology, and in clinical medicine as an antiarrhythmic drug. The United States Food and Drug Administration (FDA) approved bretylium in 1986 for "*short-term prevention and treatment of ventricular fibrillation (VF) and treatment of life-threatening ventricular arrhythmias and ventricular tachycardia (VT) unresponsive to adequate doses of a first-line antiarrhythmic agent, such as lidocaine*." Ventricular arrhythmias, including VT and VF, are the leading cause of sudden cardiac death, which represents about half of all cardiovascular mortality and accounts for over 350,000 deaths annually in the United States.[1] In 2011, the NDA sponsor withdrew bretylium from the market, largely due to unavailability of raw materials required for its production- an action deemed by the FDA to be unrelated to any safety or efficacy concerns.[2] While on the market, bretylium was part of the American Heart Association's (AHA) Advanced Cardiovascular Life Support (ACLS) treatment algorithms and guidelines; bretylium was removed from the 2000 ACLS Guidelines algorithm for VF/pulseless VT given the challenges obtaining raw materials leading to issues with the drug being manufactured.[3] Recently, bretylium has been reintroduced into the US market by a generic pharmaceutical company with the same indications as before, with the approval of an abbreviated new drug application.

Mechanism of Action

The pharmacological activity of bretylium has been well documented over the past 30 years and extensive reviews have been published.[4] Considered a class III antiarrhythmic drug by the Vaughan Williams classification, similar to amiodarone, bretylium blocks potassium channels.[5] It is known to influence the sympathetic nervous system, by selectively accumulating in the sympathetic ganglia and postganglionic adrenergic neurons when administered slowly or incrementally where it inhibits norepinephrine release by depressing adrenergic nerve terminal excitability.[6] While this latter mechanism of action plays a substantial role in the treatment of arrhythmias, it also lends itself to the development of potential side effects such as hypotension. The package insert describes multiple clinical pharmacological responses to the drug (Figure 1). The drug is poorly absorbed following oral administration and must be administered intravenously or intramuscularly. Bretylium is eliminated unchanged via the kidney and thus the dose should be reduced in patients with renal impairment.

Clinical Perspectives

Clinical trials studying bretylium are limited in terms of number and were initially performed in the 1980s; these studies were performed in a relatively small number of patients and compared either bretylium to placebo or an active comparator. Prior to this, the antifibrillatory properties of bretylium were described and the drug was administered in various clinical scenarios, including post-myocardial infarction (MI).[7]

In a randomized, double-blind study of bretylium versus placebo as a first-line antiarrhythmic drug for patients in cardiopulmonary arrest due to VF or asystole, 59 patients presenting to the Emergency Department were treated in conjunction with AHA guidelines.[8] The results indicated that those patients presenting with VF or asystole receiving

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- Suppresses ventricular fibrillation and ventricular arrhythmias, the mechanisms are not fully established.
- Electrophysiologic actions demonstrated in animal experiments:
  1. Increase in ventricular fibrillation threshold.
  2. Increase in action potential duration and effective refractory period without changes in heart rate.
- Restores injured myocardial cell electrophysiology and increases the action potential duration and effective refractory period without changing their ratio to each other - may be important factors in suppressing re-entry of aberrant impulses and decreasing induced dispersion of local excitable states.
- Selectively accumulates in sympathetic ganglia and their postganglionic adrenergic neurons where it inhibits norepinephrine release by depressing adrenergic nerve terminal excitability.
- Causes an early release of norepinephrine from the adrenergic postganglionic nerve terminals and subsequently blocks the release of norepinephrine in response to neuron stimulation.
- Positive inotropic effect on the myocardium but it is not yet certain whether this effect is direct or is mediated by catecholamine release.

Hemodynamic Effects:

- Following intravenous administration to patients with acute myocardial infarction, there was a mild increase in arterial pressure, followed by a modest decrease, remaining within normal limits throughout.
- Pulmonary artery pressures, pulmonary capillary wedge pressure, right atrial pressure, cardiac index, stroke volume index and stroke work index were not significantly changed. These hemodynamic effects were not correlated with antiarrhythmic activity.

Onset of Action:

- Following intravenous administration suppression of ventricular fibrillation is rapid, usually occurring within minutes.
- Following parenteral administration suppression of ventricular tachycardia and other ventricular arrhythmias develops more slowly, usually after 20 minutes to 2 hours.

Figure 1. Pharmacology of bretylium tosylate (truncated from package insert (6)).

bretylium compared with placebo were more likely to be successfully resuscitated (35% vs 6%; $p < 0.05$).

In a subsequent study, in the 8 months leading up to bretylium use in a specific community, 16 of 218 patients with out of hospital cardiac arrest presented with refractory VF and in all patients, defibrillation attempts were unsuccessful.[9] However, in the 16 months after bretylium went into use, of the 35 of 421 patients with out of hospital cardiac arrest due to refractory VF, 30 were defibrillated successfully. Survival to hospital discharge was 6.2% pre bretylium use versus 23% post bretylium use ($p < 0.05$).

Studies of bretylium versus standard antiarrhythmics such as lidocaine have also been conducted. In a randomized and blinded study of 146 patients with nontraumatic out of hospital VF arrest, bretylium and lidocaine yielded an organized rhythm in 89% and 93% of patients and a stable perfusing rhythm in 58% and 60% of patients, respectively.[10] Moreover, similar numbers of patients were discharged from the hospital, 34% of those given bretylium and 26% given lidocaine.

A comparative study randomized patients to receive bretylium or lidocaine as the first-line antiarrhythmic for patients in refractory VF who did not respond to the initial AHA resuscitation protocol, including defibrillation, epinephrine and sodium bicarbonate.[11] There was no significant difference between groups for rates of arriving at the Emergency Department with a pulse or survival to discharge.

Further, a randomized trial of bretylium versus high or low dose amiodarone in 302 patients with refractory VT or VF was performed.[12] The arrhythmia event rate over the first 12 hours of therapy showed comparable efficacy between the bretylium and high-dose amiodarone groups, greater than that in the low-dose amiodarone group. Mortality was similar amongst the groups but the bretylium group showed statistically more hypotension (32% in bretylium group vs 20% in high-dose amiodarone group).

Looking Forward

The re-introduction of bretylium into the marketplace is noteworthy for several reasons. First, the drug has been deemed safe and effective by the FDA and has previously been used for an identical indication. Previous studies have shown benefit of the drug to increase the number of patients who survived to hospital admission in cases of out of hospital cardiac arrest, and have shown hard outcomes similar to lidocaine and amiodarone when compared directly.

Emerging data from patients treated with bretylium in the current era of cardiac resuscitation may build upon established data and define the specific patient population who can benefit from the drug the most, for example, cardiac arrest patients with pulseless VT/VF or those with recurrent unstable VT refractory to amiodarone and/or lidocaine.

With its anti-adrenergic activity and ability to correct electrical inhomogeneity across the myocardium,[13] bretylium has been shown to be well tolerated and effective in decreasing ventricular arrhythmias in post-MI patients.[14,15] This may be explained by bretylium's influence in preventing sympathetically driven ischemia-induced coronary vasospasm as well as the ability of the drug to augment electrical signal homogeneity which may thereby prevent formation of myocardial substrate that could promote reentrant ventricular arrhythmias.

It is also useful to further examine the available randomized trials in which head to head comparisons between drugs indicated for ventricular arrhythmias have been performed. In the trials previously described in which bretylium was compared with lidocaine,[10,11] the efficacies were similar in populations with out of hospital VF where the etiology of the VF was not stated. In the randomized trial of bretylium versus amiodarone[12] the incidence of acute MI in these patients with refractory VT/VF was 6% to 10%. In a randomized trial comparing lidocaine with amiodarone[16] in patients with out of hospital refractory VF of all etiologies, amiodarone increased rates of survival to hospital admission compared with lidocaine. In a randomized trial comparing amiodarone to procainamide in inpatients with stable VT,[17] procainamide was associated with a higher rate of tachycardia termination, however patients with acute MI were excluded from this study.

Bringing together the data we have from use of bretylium in post-MI patients, our knowledge of its mechanisms of action, the fact that bretylium has shown similar efficacy when compared with lidocaine and amiodarone, and that trials studying the alternative agents for ventricular arrhythmias did not include significant numbers of patients suffering from acute MI, we believe that for these patients with ventricular arrhythmias not responding to the current agents routinely used, consideration of bretylium is reasonable as it does appear that bretylium has been more extensively tested in this population than the other available agents.

The current sponsor will have to re-introduce the drug to payers and get the drug onto formularies. A major question remains - will bretylium make it back onto the AHA's ACLS treatment algorithms and guidelines? As it stands, there are limited recommended treatment options in the face of refractory pulseless VT/VF, namely epinephrine, amiodarone, and lidocaine.[18]

Conclusion

Bretylium has returned to the market, making its way back into the treatment paradigm for patients with life-threatening ventricular arrhythmia. We anticipate that the availability of an alternative agent may improve outcomes, an expectation that will only be met with compelling clinical data.

Conflicts of interests

The authors have made the following declarations: Drs. Thind and Kowey have no conflicts of interest to declare. Dr. Sullivan is employed by Covance. Dr. Williams was employed by Covance at the time the manuscript was written. Covance provided logistical and clerical support of the project.

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