The Bretylium Saga: A Novel "Old Drug" for Cardiac Resuscitation

Dr. Marvin Bacaner returned from World War II and enrolled in Boston University Medical School then joining the University of Minnesota faculty in the Department of Physiology studying myocardial metabolism. In his studies on cardiac metabolism he would perform myocardial biopsies on dogs which caused them to develop ventricular fibrillation, which disrupted his experiments. While studying a new anti-hypertensive drug, Bretylium, he observed no episodes of ventricular fibrillation following myocardial biopsy. Dr. Bacaner stopped his experiments on myocardial metabolism and began studying bretylium as an anti-fibrillatory agent.

Following Dr. Bacaner's discovery of the anti-fibrillatory properties of bretylium,[1] Dr. Bacaner developed bretylium, during the 1960's, as a unique drug for the treatment of cardiac arrest, specifically ventricular fibrillation. Dr. Bacaner personally lead the effort to develop bretylium and conducted the clinical studies to bring bretylium to market because the pharmaceutical industry was reluctant to undertake the development of a drug that had to be given parenterally, rather than in pill form. Industry was wrong, since once bretylium was marketed, the drug became the mainstay treatment to facilitate cardiac resuscitation in the 1980's saving many lives. Bretylium is the only drug ever approved by the FDA specifically to prevent and treat ventricular fibrillation (VF). It was also approved to treat life threatening ventricular tachycardia (VT).

The FDA approval of bretylium was facilitated by the publicity bretylium received when President Dwight D. Eisenhower developed irreversible refractory VF during his sixth heart attack in 1968. His VF could not be suppressed by dozens of electric shocks or any of the then available anti-arrhythmic agents (sodium channel blockers). It was reported that Eisenhower hovered between life and death for days, barely kept alive by repeated CPR chest compressions during arrhythmic episodes. Dr. Bacaner was asked to send an emergency supply of the then investigational drug, bretylium to Eisenhower's physicians at Walter Reed Hospital in Washington, D.C. Administration of bretylium immediately stopped Eisenhower's VF episodes and saved his life. The publicity which was generated as a result of bretylium saving President Eisenhower, increased interest by the medical community in the drug and the FDA subsequently approve bretylium. In a lighter vein, Bretylium gained further attention when it was used to save the fictional character E.T. who had a cardiac arrest in Steven Spielberg's movie "E.T." (https://m.imdb.com/title/tt0083866/).

It was during this period that Dr. Bacaner came to the conclusion that anti-arrhythmic drugs were not effective in treating VF. He believed that VF treatment to be successful required unique, specific, electro-physiologic actions which bretylium possessed. Other anti-arrhythmics can be effective when DC shock terminates VF and then the drugs may prevent arrhythmia recurrence. Bretylium may terminate VF without electroshock. These findings were reported by Dr. Bacaner in a paper in 1961, establishing the anti-fibrillatory action of bretylium and its importance in the treatment of cardiac arrest.[2]

Bretylium as an anti-arrhythmic agent has some critical properties. It was first developed as an anti-hypertensive drug, known to deplete vesicular stores of catecholamines[3] thus causing a "chemical like" sympathectomy. Acute administration can initially cause a rise in blood pressure due to catecholamine release.[4] Additionally, bretylium causes an increase in the effective refractory period[5] and increases the electrical homogeneity of areas of infarcted and normal tissues.[6,7] The increased homogeneity has an anti-arrhythmic effect by reducing the substrate for ventricular tachycardia that depends on a re-entrant pathway for VT.[8] Electrical heterogeneity of the myocardium, a requisite for ventricular fibrillation substrate is modified by bretylium.[9] Bretylium in more recent studies has been found to effect the potassium channel (IKr)[10] and thus prolongs the action potential duration.[11] Bretylium is effective in increasing the ventricular fibrillation threshold in animal models,[12–14] as well as in man.[15] Thus Bretylium is effective treatment for VF and VT.[16,17]

FDA Approval

Bacaner in collaboration with Drs. John LaBree and James Breitenbucher at St. Mary's Community Hospital in Minneapolis, conducted a clinical study to determine if the routine intramuscular injection of 15 mg/kg body weight of bretylium every 6 hours over the course of 5 days would significantly reduce mortality and the incidence of VF post MI.[7] The study reported significant success of bretylium. Indeed, all-cause mortality in these MI patients treated with bretylium were significantly reduced from 15% in the control group to 3% in the prophylactic bretylium-treated group. A surprising, unexpected observation was that if bretylium was started within the first 24 hours after the onset of symptoms with acute electrocardiographic evidence of a myocardial infarction, bretylium aborted the infarction before any evidence of permanent damage to the heart occurred in one-third of patients. These observations were based on the electrocardiogram returning to normal with no increase in cardiac enzymes. In addition, complications in MI patients treated with bretylium, such as congestive heart failure, arrhythmias and cardiogenic shock were all significantly reduced compared with the control group.[7]

Along with efficacy, bretylium toxicity is limited. To produce a toxic effect in a dog, a dose of 60 mg/kg is needed, so there is a margin of safety compared with the 30 mg/kg effective dose in dogs. This dose of 30mg/kg is still considerably greater than the 5 mg/kg that is recommended in the FDA approved product label. These findings with bretylium were supported by a large clinical study from France in more than 1,500 consecutive patients with acute myocardial infarction collected over a ten year period in which bretylium was used prophylactically, given immediately upon the patient's entering the coronary care unit.[6]

https://doi.org/10.1016/j.amjcard.2020.02.010

Bacaner attributed the myocardial protective effects of bretylium to be due to its blockade of the sympathetic nervous system.[3,7]

The original FDA approvable letter for injectable bretylium to prevent and treat ventricular fibrillation was transmitted in November 1973 to Bacaner on the basis of his preclinical and human clinical studies, as well as supporting published literature on bretylium. This data included "last resort" compassionate use experience with bretylium in preventing death in patients with VF cardiac arrest. The NDA approval for bretylium was based on clinical studies using the bretylium dose of 30 mg/kg body weight. Dr. Bacaner recalled that it was unexpected that a lower dose of 5 mg/kg body weight would be recommended by the FDA "advisory committee" and subsequently by FDA in the product label. In Dr. Bacaner's studies less than a 30 mg/kg dose was not employed. When the higher dose was used, patients experienced far less hypotension as compared with subsequent reports of supine hypotensive associated with the lower dose of bretylium (5 mg/kg dose).[18] The 30 mg/kg dose has been shown to increase the survival rate from less than 0.5% to 23% for out-of-hospital cardiac arrest.[19,20] It is noteworthy that other drugs such as epinephrine and sodium-channel blocking anti-arrhythmic drugs such as lidocaine are not FDA approved for the treatment of VF cardiac arrest.

Updating the Bretylium Story

With the introduction of IV amiodarone, the use of bretylium declined. Since bretylium was a difficult drug to manufacture and the FDA increased the requirements for drug manufacturers for parenteral agents; bretylium became unavailable in the year 2000. While in a "head-to-head" study of amiodarone and bretylium, the drugs were equally effective, bretylium caused more hypotension with the FDA recommended lower dose of 5 mg/kg.[18] With more hypotension reported with Bretylium use[6] and the shortage of drug substance, bretylium became unavailable for clinical use. Its scarcity led to the drug being dropped from ACLS guidelines. With the aid of Dr. Bacaner, Academic Pharmaceuticals obtained a new reliable, long term supply of drug substance and obtained FDA approval for the remarketing of bretylium (December 2018). Given the drug's decade long absence, it seems appropriate to use bretylium to treat ventricular fibrillation unresponsive to first line treatment with amiodarone and DC shock at the approved dose of 5 mg/kg initially, followed by an additional 5 mg/kg if the first dose fails. Further studies are needed to determine the optimum dose and if indeed higher doses of bretylium are more effective with less hypotension. While hypotension can usually be dealt with by volume expansion by administering IV fluids, the ability to avoid hypotension by employing a higher bretylium dose would be important information and at times a preferred approach. The past observations with the higher dose would need support by contemporaneous trials. That the higher doses recommended by Bacaner cause less hypotension is plausible because of greater catecholamine release by bretylium though displacement of catecholamines from storage vessels resulting in an increase in heart rate and vasoconstriction, counteracting the direct vasodilator effects of the drug. Additionally, bretylium's inotropic action may also compensate for vasodilation by increasing cardiac output.[21]

Addendum

During the preparation of this manuscript, after receiving notification of the FDA re-approval of bretylium, Dr. Marvin Bacaner died at age 96, still strongly advocating for bretylium use in cardiac arrest resuscitation.

Disclosures

Doctor Somberg has a financial interest in Academic Pharmaceuticals, which developed Bretylium and transferred ownership of the NDA to Pharmaceutical International (Pii).

Marvin Bacaner, MD[a]
John Somberg, MD[b,*]
[a] *Professor Emeritus, University of Minnesota, Minneapolis, Minnesota*
[b] *Professor Emeritus Cardiology, Pharmacology and Clinical Pharmacology, Rush University, Chicago, Illinois*
[*] Corresponding author: Tel: (847) 735-1170; fax: (847) 735-1173.
(jsomberg@rush.edu).

1. Bacaner MB. Quantitative comparison of bretylium with other antifibrillatory drugs. *Am J Cardiol* 1968;21:504–512.
2. Bacaner M. Bretylium tosylate for suppression of induced ventricular fibrillation. *Am J Cardiol* 1966;17:528–534.
3. Mizgala HF. Newer drugs in the treatment of hypertension. *Can Med Assoc J* 1965;92:918–922.
4. Markis JE, Koch-Weser J. Characteristics and mechanism of inotropic and chronotropic action of bretylium tosylate. *J Pharmacol Exp Ther* 1971;178:94–102.
5. Heissenbuttel RH, Bigger JT. Bretylium tosylate: a newly available antiarrhythmic drug for ventricular arrhythmias. *Ann Intern Med* 1979;91:229–238.
6. Torresani J. Bretylium tosylate in patients with acute myocardial infarction. *Am J Cardiol* 1984;54:21A–25A.
7. Bacaner M, Brietenbucher J, LaBree J. Prevention of ventricular fibrillation, acute myocardial infarction (myocardial necrosis), heart failure, and mortality by bretylium: is ischemic heart disease primarily adrenergic cardiovascular disease? *Am J Ther* 2004;11:366–411.
8. Sasyniuk BI. Symposium on the management of ventricular dysrhythmias. Concept of reentry versus automaticity. *Am J Cardiol* 1984;54:1A–6A.
9. Bacaner MB. Treatment of ventricular fibrillation and other acute arrhythmias with bretylium tosylate. *Am J Cardiol* 1968;21:530–543.
10. Bacaner MB, Clay JR, Shrier A, Brochu RM. Potassium channel blockade: a mechanism for suppressing ventricular fibrillation. *Proc Natl Acad Sci USA* 1986;83:2223–2227.
11. Swissa M, Qu Z, Ohara T, Lee MH, Lin SF, Garfinkel A, Karagueuzian HS, Weiss JN, Chen PS. Action potential duration restitution and ventricular fibrillation due to rapid focal excitation. *Am J Physiol Heart Circ Physiol* 2002;282:H1915–H1923.
12. Euler DE, Scanlon PJ. Mechanism of the effect of bretylium on the ventricular fibrillation threshold I dogs. *Am J Cardiol* 1985;55:1396–1401.
13. Holland K, Patterson E, Lucchesi BR. Prevention of ventricular fibrillation by bretylium in a conscious canine model of sudden coronary death. *Am Heart J* 1983;105:711–717.
14. Anderson JL, Patterson E, Conlon M, Pasyk S, Pitt B, Lucchesi BR. Kinetics of antifibrillatory effects of bretylium: correlation with myocardial drug concentrations. *Am J Cardiol* 1980;46:583–592.

15. Bacaner MB. Experimental and clinical effects of bretylium tosylate on ventricular fibrillation, arrhythmic and heart block. *Geriatrics* 1971;26:132–148.
16. Cohen HC, Gozo EG Jr, Langendorf R, Kaplan BM, Chan A, Pick A, Glick G. Response of resistant ventricular tachycardia to bretylium. Relation to site of ectopic focus and location of myocardial disease. *Circulation* 1973;47:331–340.
17. Bacaner MB. Quantitative comparison of bretylium with other antifibrillatory drugs. *Am J Cardiol* 1968;21:504–512.
18. Kowey PR, Levine JH, Herre JM, Pacifico A, Lindsay BD, Plumb VJ, Janosik DL, Kopelman HA, Scheinman MM. Randomized, double-blind comparison of intravenous amiodarone and bretylium in the treatment of patients with recurrent, hemodynamically destabilizing ventricular tachycardia or fibrillation. The Intravenous Amiodarone Multicenter Investigators Group. *Circulation* 1995;92:3255–3263.
19. Arcidiacono R. Use of bretylium tosylate in ventricular fibrillation. *Clin Ter* 1978;84:253–266.
20. Tacker WA Jr, Niebauer MJ, Babbs CF, Combs WJ, Hahn BM, Barker MA, Seipel JF, Bourland JD, Geddes LA. The effect of newer antiarrhythmic drugs on defibrillation threshold. *Crit Care Med* 1980;8:177–180.
21. Bacaner M. Interaction of calcium, norepinephrine and bretylium in antagonizing myocardial depression caused by anti-arrhythmic drugs. *Mt Sinai J Med* 1970;37:247–255.