

REVIEW

Newer Antiarrhythmic Agents for Atrial Fibrillation: Shall we Eventually do away with Proarrhythmia?

Anthony M. Sideris, MD

2nd Department of Cardiology,
Evangelismos General Hospital of
Athens, Athens, Greece

ABSTRACT

Despite advances in drug therapy for the treatment of atrial fibrillation (AF), there continues to be a need for antiarrhythmic agents that have improved safety and efficacy profile. Unfortunately, drugs that block the potassium channels or are multichannel blockers, although they may be effective antiarrhythmics, they delay repolarization and thus they confer a proarrhythmic effect by inducing torsade de pointes, a potentially lethal ventricular arrhythmia. Most newer antiarrhythmic drugs are potassium channel blockers and this limits their usefulness. A less toxic agent compared to amiodarone, the noniodinated analogue of amiodarone (dronedarone) is being investigated; however, it appears already unsafe in patients with heart failure. Future antiarrhythmic agents will probably be atrial-selective blocking agents without affecting repolarization in the ventricular myocardium and thus avoid ventricular proarrhythmia with its attendant life-threatening consequences.

KEY WORDS: *antiarrhythmic agents; atrial fibrillation; proarrhythmia; torsade de pointes; atrial selective blockers*

INTRODUCTION

Despite advances in drug therapy for the treatment of atrial fibrillation (AF), there continues to be a need for antiarrhythmic agents that have improved safety and efficacy profile.¹⁻⁷ The wavelength in the atrium plays a critical role in AF. The two fundamental mechanisms of antiarrhythmic drugs in terminating AF include slowing of conduction and lengthening of repolarization and refractoriness. In the wake of the CAST trial demonstrating the proarrhythmic properties of agents with selectivity for sodium channels, when used as antiarrhythmic drugs in patients with significant underlying structural heart disease, attention switched to drugs inhibiting potassium channels. They terminate and/or prevent AF by lengthening action potential duration and the effective refractory period. Unfortunately, drugs that delay repolarization can induce polymorphic ventricular tachycardia in the form of torsade de pointes, a potentially lethal proarrhythmic effect.

ABBREVIATIONS

ACC = American College of Cardiology
AF = atrial fibrillation
AHA = American Heart Association
ESC = European Society of Cardiology
TdP = torsade de pointes

Correspondence to:
Anthony Sideris, MD
2nd Department of Cardiology
Evangelismos Hospital
Athens, Greece
E-mail: asideris@hol.gr

CLASS III ANTIARRHYTHMIC DRUGS

DOFETILIDE

The antiarrhythmic effects of dofetilide^{8,9} are due to its ability to block the fast component of the repolarizing potassium current I_{Kr} , resulting in an increase of the action potential duration and prolonged effective refractory period without altering conduction velocity. The drug half-life is 8 to 10 hours, and steady-state plasma concentrations are achieved within two to three days. Approximately 80% of dofetilide is renally eliminated. Dofetilide has been shown to be effective for the treatment of AF or atrial flutter in patients with structural heart disease, with neutral effects on mortality. Although free of noncardiac adverse effects, dofetilide is associated with proarrhythmic effects, primarily torsade de pointes (TdP) which has been reported to range in frequency from 0.6 to 2.9%. The risk of TdP increases when dofetilide is administered to patients with a prolonged baseline QT interval, electrolyte abnormalities, or renal impairment without dosage adjustment. Most cases of TdP occur during the first 3 days of treatment. Therefore, FDA has mandated that patients started or restarted on dofetilide therapy should be placed, for a minimum of three days, in a facility that can provide creatinine clearance calculations, continuous electrocardiographic (ECG) monitoring, and cardiac resuscitation. Data from clinical studies, which enrolled about 1000 patients, demonstrated that conversion to sinus rhythm occurs in 30% of patients, but these data are mainly related to long-lasting AF episodes. In addition to being an effective agent for medical conversion of AF to sinus rhythm, dofetilide had a 58% efficacy rate in maintaining sinus rhythm at 1-year postcardioversion compared with only 25% in the placebo group in the SAFIRE-D trial.⁹ Results for maintaining sinus rhythm in the EMERALD trial were similar.⁹ In both trials, efficacy was dose related. According to the recent ACC/AHA/ESC treatment guidelines for AF,¹⁰ dofetilide and amiodarone are the two drugs suggested for use in patients with heart failure.

IBUTILIDE

Ibutilide^{11,12} is a novel antiarrhythmic agent that prolongs action potential duration by enhancing sodium exchange during phase 2 of the action potential with a lesser effect in blocking the outward potassium current (I_{Kr}). It is available only as an intravenous agent. Ibutilide is metabolized extensively in the liver. The half-life of ibutilide and its metabolite is 4 to 8 hours. It appears to work better in patients with AF of relatively recent onset and has greater efficacy in atrial flutter. In a prospective comparative trial, ibutilide was more effective than procainamide and reverted 35 to 40% of patients to sinus rhythm within 1 hour of administration, compared with only 20% of the procainamide group. In another study, ibutilide was more effective than sotalol in terminating AF.

Its use must be strictly monitored with ECG because of the risk of torsade de pointes (1-5% of cases), which occurs more often in female patients, and in the presence of heart failure, hypokalemia, long QT at baseline ECG and organic heart disease. Although ibutilide is hemodynamically well tolerated in patients with ventricular dysfunction, the incidence of torsade de pointes is increased in patients with an ejection fraction of <35% and therefore must be used with caution in this setting. Ibutilide can also be used to lower the cardioversion energy requirement in patients refractory to cardioversion. The drug has been shown to have an enhanced efficacy in AF or atrial flutter conversion when added to propafenone.

AZIMILIDE

Azimilide,¹³⁻¹⁵ an antiarrhythmic agent with Vaughan-Williams class III activity, blocks fast and slow components of the cardiac delayed rectifier potassium channels. The properties of azimilide differ somewhat when compared with other pure Class III agents in terms of the drug's effect relative to changes in heart rate (use dependence). Azimilide has a long elimination half-life of 114 hours, and is hepatically cleared. Recent data from the ALIVE trial has shown that azimilide has neutral effect on survival in a high-risk post-myocardial infarction population. Randomized, placebo-controlled clinical trials have shown that it was effective in patients with AF in prolonging the time to symptomatic arrhythmia recurrence. Azimilide was given to patients with a broad range of associated heart diseases including congestive heart failure and ischemic heart disease. The most effective dose appears to be 125 mg/day, with efficacy rates of about 50%. Azimilide prolongs the QTc on the ECG and is associated with infrequent cases of torsade de pointes (0.9%). A low incidence of drug-induced neutropenia has been reported.

DRONEDARONE

Dronedarone¹⁶⁻¹⁸ is a benzofuran derivative, structurally related to amiodarone, i.e. the noniodinated analogue of amiodarone. It has an electrophysiologic profile similar to that of amiodarone, but its lack of iodine makes it a promising alternative to amiodarone. To date, end organ toxicity has not been reported. Dronedarone has an elimination half-life of 24 hours, with steady-state levels being achieved in 5 to 7 days. It is an I_{Kr} , I_{Ks} , I_{to} , fast sodium and calcium antagonist. Dronedarone is a potent inhibitor of the acetylcholine-activated K^+ current and like amiodarone shows an antiadrenergic action. It prolongs action potential duration in the atria and ventricles, slows sinus rate and prolongs AV nodal refractory period. In the Dronedarone Atrial Fibrillation Study After Electrical Cardioversion (DAFNE) trial, dronedarone 800 mg/day appeared to be effective and safe for the prevention of AF relapses after cardioversion. The Antiarrhythmic Trial in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) trial was stopped due

to potential increased risk of death in the dronedarone group. Trials of dronedarone in the maintenance of sinus rhythm in patients with AF or flutter (EURIDIS, ADONIS)¹⁸ have shown that dronedarone was more effective than placebo in maintaining sinus rhythm and in reducing the ventricular rate during recurrence of AF.

TEDISAMIL

Tedisamil,¹⁹ is different from other pure Class III antiarrhythmic agents, because it blocks a complex aggregate of repolarizing ionic currents, has anti-ischemic properties, and slows the heart rate. Intravenous tedisamil rapidly converts recent onset AF. However, the program for tedisamil was temporarily interrupted because of concerns over the drug's possible proarrhythmic effects.

FUTURE ANTIARRHYTHMIC DRUGS

5-HT₄ receptors are present in human atrial cells and when stimulated may cause atrial arrhythmias. Antagonists to 5-HT₄ receptors have been developed (piboserod, SB203186) and currently are being used in clinical trials. It is unknown at this time, whether this drug class will have a clinical role.

Certain potassium channels such as ultrarapid delayed rectifier (I_{Kur}) and acetylcholine-sensitive potassium channel (I_{KACh}) are predominantly present in the atria and marginally present or absent in the human ventricle and play an important role in the atrial resting potential. Therefore, antiarrhythmic drugs, atrial-selective agents that modify the function of these channels could be important for the treatment of supraventricular arrhythmias, without the potential risk of inducing ventricular arrhythmias. The *selective I_{Kur} blockers* S1185, S9947, S20951, and RSD1235 (vernakalant)^{20,21} effectively decreased atrial vulnerability in animals by preferentially increasing left atrial refractory period. In contrast to dofetilide, azimilide, and sotalol, they did not prolong ventricular refractoriness. Another promising antiarrhythmic drug under development is AVE0118. This I_{Kur} and I_{to} blocker preferentially increased atrial refractoriness in electrically remodeled atria and was able to convert persistent AF without lengthening the QT interval.

Another target that may be useful for future antiarrhythmic drug action is the stretch activated-channels caused by hemodynamic changes, which are believed to be involved in the genesis of some arrhythmias. It has been recently shown that the peptide GsMtx-4, found in the venom of the tarantula *Grammostola spatulata*, could selectively block cationic stretch-activated channels in cardiac myocytes and reduce the incidence and the duration of AF episodes that are induced by bursts of rapid atrial stimulation. Data from animal studies showed that gadolinium chloride suppressed stretch-activated arrhythmias. Unfortunately, gadolinium chloride is toxic to

the heart because of its nonselective displacement of calcium and other ions from membrane sites, and thus cannot be used as an antiarrhythmic agent. ZP123 which facilitates conduction in the gap junction and drugs that are long-lasting A-1 adenosine antagonists are under development.

Finally, based on the molecular and cellular investigations of the mechanisms involved in the initiation and maintenance of AF, novel approaches, mainly targeting the intracellular calcium overload, are currently being investigated.

It is clear that we need better antiarrhythmic drugs with less attendant cardiac and organ toxicity. Several new agents are under investigation and the impact they will have on AF management remains to be seen.

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