Atrial Fibrillation—New Antiarrhythmic Drugs

Currently available antiarrhythmic drugs for the treatment of atrial fibrillation are limited in their efficacy and have potential for adverse effects, including torsade de pointes. With the aging of the population, the incidence of atrial fibrillation will double in frequency over the next 15 years. Thus, more effective and safer antiarrhythmic drugs for the treatment of atrial fibrillation are needed.

Attempts to modify the most effective antiarrhythmic, amiodarone, have resulted in the development of other multichannel blockers including dronedarone, celivarone, and ATI-2042.1 Targeting blockade of the ultra-rapid potassium rectifier current (I_{Kur}) and the acetylcholine-dependent potassium current (I_{KACCH})—which exists only in atrial tissue—is more atrial-specific and, theoretically, would eliminate the risk of torsade de pointes. This atrial-selective approach has been the goal of vernakalant and other new antiarrhythmics.1,2 Intravenous tedisamil, another potassium channel-blocking agent, and the gap junction facilitating agent rotigaptide are also under development.1

Investigational Antiarrhythmic Agents for Cardioversion of Atrial Fibrillation

Tedisamil

Tedisamil is a class III agent that slows sinus rate, possesses antiischemic and anti-ischemic properties, and blocks rapid delayed rectifier outward potassium current (I_{Kur}), transient outward potassium current (I_{to}), slowly activating delayed rectifier potassium current (I_{Ks}), I_{Kur}, adenosine tri-phosphate (ATP)-activated potassium current (I_{KATP}), and fast sodium current (I_{Na}).3 Tedisamil lengthens the action potential and effective refractory periods in both the atria and the ventricles.3 Tedisamil has completed phase III trials to establish an indication for conversion of atrial fibrillation. Hohnloser et al. investigated the use of tedisamil versus placebo for treating atrial fibrillation/atrial flutter patients with onset of less than 48 hours.4 In the placebo-treated patients with atrial fibrillation, four of 46 (9%) converted to sinus rhythm. Treatment with tedisamil 0.4mg/kg converted atrial fibrillation to sinus rhythm in 24 of 52 patients (46%), and in 24 of 42 patients (57%) in the 0.6mg/kg group (p<0.001 for both tedisamil groups versus placebo). Conversion to sinus rhythm occurred with a mean time to conversion of 35±27 minutes for the 0.4mg/kg dose and 34±21 minutes for the 0.6mg/kg dose. The number of patients who remained in sinus rhythm at 24 hours after the dose of tedisamil was also significantly greater in the treated group relative to the placebo group. Tedisamil prolonged the corrected QT (QTc) interval in a dose-dependent fashion, becoming statistically significant at a dose of 0.6mg/kg (QTc increased 16.9±45.2 from a baseline of 443.1msec; p=0.037). At a dose of 0.4mg/kg, the QTc slightly lengthened (10.8±45.9msec), but did not reach statistical significance. In the same study, tedisamil's efficacy in converting atrial flutter to sinus rhythm was quite low. Tedisamil's effects on prolonging the QT interval and case reports of torsade de pointes may be of similar concern to those of ibutilide. Ibutilide appears to be much more effective in terminating atrial flutter. Tedisamil is currently undergoing review at the US Food and Drug Administration (FDA).

Vernakalant Hydrochloride (RSD1235)

Vernakalant hydrochloride (RSD1235) is an atrial-selective (I_{KACCH}, I_{to}, I_{Kur}) potassium channel blocker that has little effect on ventricular repolarization and a frequency- and voltage-dependent I_{Na} blocking activity.6,7 In humans, vernakalant appears to prolong atrial-effective refractory periods with no significant effect on ventricular repolarization.7

Intravenous vernakalant has rapid elimination when used intravenously, with a half-life of 2.9–3.3 hours.5 Vernakalant is primarily metabolized by the cytochrome (CYP) P450 system (CYP2D6). The demethylated metabolites have some bioactivity, but these are rapidly conjugated, inactivated, and eliminated by renal excretion. Intravenous dosing is 3mg/kg infused over 10 minutes followed by 2mg/kg, if atrial fibrillation persists.

In the Controlled Randomized Atrial Fibrillation Trial (CRAFT), patients (n=56) with atrial fibrillation of three to 72 hours duration were treated with RSD-1 0.5mg/kg followed by 1mg/kg (n=18) versus RSD-2 2mg/kg followed by 3mg/kg (n=18) versus placebo (n=20). The RSD-2 group was superior to placebo for termination of atrial fibrillation (61 versus 5%, p=0.0005), patients in sinus rhythm at 30 minutes (56 versus 5%; p<0.001) and one hour (53 versus 5%; p=0.0014), and median time to conversion (14 versus...
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162 minutes; p=0.016). No serious adverse events, including torsade de pointes, were noted.

Similar efficacy data have been reported in a larger group of patients in the Atrial arrhythmia Conversion Trial (ACT)-1. The ACT-1 was a phase III trial comparing intravenous vernakalant with placebo in 416 patients with atrial fibrillation onset with duration of three to seven days. Of the patients with recent-onset atrial fibrillation (duration three hours to seven days), 52% converted to sinus rhythm compared with 4% of placebo patients (p<0.001). However, in the overall study, when one looked at the atrial fibrillation duration of three hours to 45 days, only 38% of patients receiving intravenous vernakalant had their atrial fibrillation terminated compared with 3% of placebo patients (p<0.001). Intravenous vernakalant was ineffective in converting atrial flutter, with only one of 39 drug-treated patients converting compared with 0 of 15 atrial flutter patients treated with placebo. No drug-related torsade de pointes was noted.

ACT-2 evaluated the efficacy and safety of intravenous vernakalant for the treatment of 190 patients who developed atrial fibrillation or atrial flutter between 24 hours and seven days following coronary artery bypass graft or valve replacement surgery. In the atrial fibrillation group, 47% of patients dosed with intravenous vernakalant converted to sinus rhythm within 90 minutes compared with only 14% of placebo patients (p=0.0001). The median time to conversion was around 12 minutes for the vernakalant responders. Similar to the other two ACT trials, no torsade de pointes was reported and 0 out of 10 patients who had atrial flutter converted to sinus rhythm with intravenous vernakalant.

In addition to the above trials, ACT-4 is a phase III study evaluating the safety of intravenous vernakalant in about 120 patients with atrial fibrillation.

The most common non-cardiac side effects noted with intravenous vernakalant are dysgeusia, paresthesia, nausea, cough, pruritus, and sneezing. Hypotension has also been noted in a small number of patients.

Compared with ibutilide, intravenous vernakalant studies included patients who had atrial fibrillation recurrences on oral antiarrhythmic agents. Although intravenous vernakalant appears to have much less proarrhythmic potential, it lacks efficacy in converting atrial flutter. Intravenous vernakalant is currently being reviewed by the FDA for consideration for market approval in the US.

A sustained-release oral preparation of vernakalant has been developed. A phase IIa trial demonstrated that oral vernakalant at 300 and 600mg twice daily was superior to placebo in maintaining sinus rhythm after cardioversion of persistent atrial fibrillation over a 28-day treatment. In the placebo group, 57% of patients had atrial fibrillation recurrence compared with 39% in the vernakalant 300mg twice-daily group (p=0.048) and 39% in the 600mg twice-daily group (p=0.06). A similar trial is ongoing to assess the role of 150, 300, and 500mg of oral vernakalant twice daily in maintaining sinus rhythm after cardioversion of persistent atrial fibrillation. This placebo-controlled trial will have a 90-day follow-up and help with further dose ranging to plan phase III efficacy trials in paroxysmal and persistent atrial fibrillation.

New Multichannel Amiodarone Analog
Antiarrhythmic Agents

Dronedarone

Dronedarone is an amiodarone-like compound without the iodine moiety. To date, thyroid, pulmonary, or hepatic end-organ toxicity has not been reported. Electrophysiologically, dronedarone blocks I Kr, I Ks, I to, and fast sodium and calcium channels. Dronedarone prolongs the action potential duration in the atria and ventricles with no significant reverse-use dependence. Other electrophysiological effects similar to amiodarone include alpha-, beta-, and muscarinic-blocking effects. Dronedarone appears to slow sinus rates less than amiodarone, but prolongs atrioventricular (AV) nodal refractory periods and thus is useful as a rate-control agent. Similar to amiodarone, dronedarone increases the QT interval, but torsade de pointes has not yet been reported, possibly due to the fact that dronedarone reduces the transmural dispersion of ventricular refractoriness and protects from class III antiarrhythmia induced soon after depolarizations.

Dronedarone has a half-life of 27–31 hours with steady state being achieved within seven to 10 days. It is primarily metabolized by CYP-3A4, and is both an inhibitor and a substrate of the enzyme. The N-debutyl metabolite exhibits one-third to one-tenth of the pharmacodynamic activity of the parent compound. Similar to amiodarone, dronedarone causes increases in the levels of simvastatin and digoxin. However, no significant dronedarone–warfarin interaction has been noted.

In the Dose Adjustment For Normal Eating (DAFNE) trial, dronedarone 400mg twice daily was superior to placebo in preventing recurrent atrial fibrillation. The median time to recurrence was 59.9 days in the dronedarone group compared with 43.7 days in the placebo group (p=0.033; relative risk (RR) 0.45; confidence interval (CI) 0.28–0.72). Higher doses (800 and 1,600mg twice daily) of dronedarone were ineffective and were associated with a higher incidence of gastrointestinal subjective adverse effects.

The American–African trial with Dronedarone In atrial fibrillation or flutter for the maintenance of Sinus rhythm (ADONIS) and EURopean trial In atrial...
fibrillation or atrial flutter patients receiving Dronedarone for the maintenance of Sinus rhythm (EURIDIS) both demonstrated that dronedarone significantly (p<0.05) suppressed recurrent atrial fibrillation at a dose of 400 mg twice daily. In EURIDIS, the median time to first arrhythmia recurrence was 2.3 times longer in the dronedarone group with a 22% reduction in atrial fibrillation/flutter recurrences compared with placebo. In ADONIS, the median time to arrhythmia recurrence was close to three times longer, and there was a 28% reduction of atrial fibrillation/flutter recurrences compared with the placebo arm of the study. Data from these trials and the Efficacy and safety of Dronedarone for The cOntrol of ventricular rate (ERATO) trial provide statistical evidence that dronedarone, similar to amiodarone, has the ability to slow the ventricular response if atrial fibrillation/flutter recurs.  

The Antiarhythmic trial with Dronedarone in Moderate to Severe congestive heart failure Evaluating morbidity Decrease (ANDROMEDA), studying the safety of dronedarone in patients with severe left ventricular dysfunction, was prematurely terminated due to higher mortality in the arrhythmia-treated arm of the study. This adverse effect may be secondary to the withdrawal of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, given that the dronedarone increases the tubular secretion of creatinine with no effect on creatinine clearance. The primary efficacy objective of this study was the reduction of deaths from any cause or hospitalizations for worsening heart failure in patients with moderate to severe congestive heart failure (CHF) and left ventricular dysfunction over a minimum period of 12 months compared with placebo.

A large placebo-controlled trial, ATHENA, has completed enrollment of over 4,500 atrial fibrillation patients with risk factors for stroke. The primary composite end-point is reducing mortality and hospitalizations. The results of ATHENA should be available in 2008, and will determine whether the FDA will approve dronedarone.

Other Amiodarone Analog Compounds

Cellvarone (SSR149744C) is a drug with similar electrophysiological effects to dronedarone. An early phase II human trial with oral cellvarone reported no dose effect (50, 100, 200, 300 mg daily) in preventing the recurrence of persistent atrial fibrillation post-cardioversion. The 50 mg daily dose had a recurrence rate of 52.1% at three months compared with 67.1% for placebo patients (p=0.055). No torsade de points was reported in this study.

Phase II trials with another amiodarone-like compound, ATI-2042, are ongoing, assessing the ability of this compound to suppress atrial fibrillation in patients with pacemakers.

Gap Junction Modulators

**Rotigaptide**

Gap junction (connexin) modulators such as rotigaptide (ZP123) offer promise for the treatment of atrial fibrillation. Loss of cell contact is important for the genesis of atrial arrhythmias. Thus, conduction slowing and gap junction uncoupling may be substrates for atrial fibrillation. Mutations in GJAS, the gene encoding connexin 40, may predispose impairment of gap junction assembly or uncoupling in certain predisposed patients. Thus, restoration of inter-cellular conduction may prevent atrial conduction slowing in certain pathological states. This compound has demonstrated this favorable effect in a rat model of metabolically stress-induced changes. Rotigaptide has been demonstrated to reduce atrial fibrillation vulnerability in a canine model of chronic mitral regurgitation but not in a ventricular tachy-pacing model that results in atrial fibrosis. This drug reduced atrial fibrillation in a canine model of atrial ischemia.

Identification of those patients who will benefit from improving gap junction conduction will require further study.

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