Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in over 2% of the general population. Its incidence increases with advanced age, and more than 9% of octogenarians have this disorder. AF presentations are also being encountered more frequently in emergency departments, with subsequent hospital admission rates approaching 60%. The effect of AF on health care resources is a growing concern, and a streamlined, efficacious, and safe approach to treating AF patients is greatly needed.

Currently, there are 2 strategies for managing AF: (1) attempting to maintain the patient in sinus rhythm or (2) controlling the ventricular response rate. Older and asymptomatic patients generally receive rate-control treatments, while conversion to sinus rhythm may be the preferred initial approach in active, symptomatic, or younger patients. In this latter group of patients and in cases where the strategy is not clear, variable efficacy and extensive side effects limit the usefulness of currently available antiarrhythmic medications. Newer drugs are being developed and will ideally provide a safer and more effective option to combat AF.

In December 2007, the US Food and Drug Administration (FDA) Cardiovascular and Renal Drugs Advisory Committee evaluated 2 new antiarrhythmic medications, both intended for the rapid conversion of AF. The group unanimously voted against approving intravenous tedisamil, while voting 6 to 2 in favor of approving vernakalant (Kynapid). Although these drugs are both novel class III antiarrhythmics, the FDA voted to approve vernakalant based on what the committee viewed as significant differences in safety profiles and in patient populations studied (applicability to the US market); thus, it is possible that vernakalant will be the first new antiarrhythmic medication to hit the US market in almost a decade.

Pharmacology of AF converting medications

The currently evaluated antiarrhythmic agents for the conversion of AF to normal sinus rhythm include Vaughn Williams class Ia, class Ic, and class III antiarrhythmics. Class Ia (procainamide [Pronestyl], quinidine [Quinaglute]) and class Ic (flecainide [Tambocor], propafenone [Rhythm]) agents interrupt AF by blocking the inward sodium current (INa) to reduce conduction velocity. Class Ic agents also demonstrate rate-dependent inhibition, resulting in an increase in efficacy when the atrial depolarization rate is high. This is different from class III agents, such as amiodarone (Cordarone) and ibutilide (Corvert), which inhibit the rapidly and ultra-rapidly activating potassium currents, IKr and IKur, respectively. This increases the action potential duration, enhances refractoriness, and increases the length of reentrant wavelengths that are responsible for sustaining AF, ultimately terminating the arrhythmia. While all currently available antiarrhythmic agents are atrial repolarization delaying agents (ARDas), they do not increase the atrial conduction velocity. Vernakalant is also referred to as an ARDA, but is actually considered a multichannel activator.
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blocker with varying pharmacologic effects.

Like other class III antiarrhythmic medications, IK$_{ur}$ is the main target of vernakalant, but its mechanism of action also involves blockade of transient outward currents and sodium ion channels.\(^5\) The selectivity for IK$_{ur}$ compared with IK$_{s}$, IK$_{r}$, and INa blockade may impart atrial selectivity and less proarrhythmia across all heart rates compared with other antiarrhythmic medications.\(^4\)

**Pharmacokinetics**

The published literature is scarce with regard to the pharmacokinetics, pharmacodynamics, and drug interactions of vernakalant, but small phase 2 trials have shed some light on these issues. Vernakalant has demonstrated linear pharmacokinetics in the dosage range of 0.1 to 5 mg/kg. The oral bioavailability of this agent is estimated to be 20%. Vernakalant follows a two-compartment pharmacokinetic model, achieving nearly complete distribution within 30 minutes and undergoing rapid first-order eliminations ($t_{1/2}$ = 3-6 minutes).\(^1\) A study by Moe and colleagues found that after a single dose, maximum plasma concentrations ranged from 0.08 to 4 mcg/mL, and the area under the curve was approximately 12 mcg(h)/mL.\(^6\)

Vernakalant is hepatically metabolized by cytochrome P$_{450}$2D6 (CYP$_{450}$2D6) and has an estimated elimination half-life of 2 to 3 hours. The plasma concentration of vernakalant may be increased in patients who are poor metabolizers or in those taking concomitant inhibitors of the 2D6 isoenzyme. Although evaluation samples have been small, age, renal impairment, hepatic insufficiency, and heart failure did not demonstrate a significant effect on the pharmacokinetic profile. Comparison of these parameters as well as others between vernakalant and other medications used for cardioversion are included in the Table.

**Safety**

Recent evaluations of antiarrhythmic drug safety for drug design and regulatory approval have focused on the potential of the agent to prolong ventricular repolarization time and induce torsade de pointes. Vernakalant was not thought likely to cause ventricular arrhythmias, as the IK$_{ur}$ receptor has only been identified in atrial tissue.\(^7\) Early clinical investigations did not demonstrate drug-induced QT prolongation with vernakalant and even found it protective against clofilium-induced torsade de pointes in one animal model.\(^9\)

Larger evaluations of the safety and efficacy of vernakalant were performed in the 4 phase 3 ACT (Atrial Arrhythmia Conversion Trial) trials. To date, data from ACT 1, 2, and 3 have been presented at major meetings, but the only published, peer-reviewed trial was ACT 1. ACT 4 is an open-label safety trial evaluating vernakalant for new-onset AF. The trial aims to corroborate clinical safety data obtained thus far. Enrollment in ACT 4 is complete, and data from the trial were used in the submission to the FDA. In ACT 1, no patients experienced torsade de pointes within the first 24 hours of infusion.\(^10\) In addition, no significant difference was detected in QRS or QTc intervals relative to patients receiving placebo. Pooled data from all 4 ACT trials indicated that the incidence of ventricular arrhythmia observed on continuous electrocardiographic monitoring within the first 24 hours of infusion was 16.5% in patients receiving placebo ($n = 315$), 12.9% in patients receiving 1 dose of vernakalant ($n = 241$), and 12.3% in patients receiving 2 doses of vernakalant ($n = 496$).\(^11\) In all phase 2 and 3 trials conducted, only 1 patient receiving vernakalant experienced torsade de pointes, but this incidence was thought to result from previous administration of ibutilide (Corvert).\(^11\)

While vernakalant does not
appear to prolong the QT interval or cause excess ventricular arrhythmias, a number of adverse events were identified in clinical trials. In a pooled analysis of all phase 2 and 3 trials, hypotensive adverse events within 2 hours of dosing were increased in patients receiving vernakalant compared with placebo (5.4% vs 1.0%). Hypotensive events did not appear to persist beyond 2 hours. The most frequently reported adverse events in patients receiving vernakalant were dysgeusia (20.4%), sneezing (15.0%), paresthesia (8.8%), and nausea (6.5%). Bradycardia and atrioventricular block were also observed more frequently in those receiving vernakalant compared with placebo, but this could be a result of more successful conversion to sinus rhythm in the presence of rate-controlling agents.

Of note, while some patients with systolic dysfunction were represented in phase 3 trials, more severely ill and hemodynamically unstable individuals who may require electrical cardioversion for

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Amiodarone</th>
<th>Dronedarone</th>
<th>Flecainide</th>
<th>Ibutilide</th>
<th>Vernakalant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Beta-receptor blocker, K+ channel blocker, Na+ channel blocker, Ca+ channel blocker</td>
<td>Beta-receptor blocker, alpha-receptor blocker, K+ channel blocker, Na+ channel blocker, Ca+ channel blocker</td>
<td>Slow Na+ channel blocker</td>
<td>Beta-receptor blocker and agonist, alpha-receptor blocker and agonist, K+ channel blocker</td>
<td>K+ channel blocker, Na+ channel blocker, with atrial selectivity</td>
</tr>
<tr>
<td>Oral bioavailability</td>
<td>~50%</td>
<td>15%-20% (increased 2-fold with food)</td>
<td>70%-95% (may be decreased with antacids)</td>
<td>Not available</td>
<td>~20%</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>~60 L/kg</td>
<td>~12 L/kg</td>
<td>4.9-10 L/kg</td>
<td>9-13 L/kg</td>
<td>Unknown</td>
</tr>
<tr>
<td>Route of elimination</td>
<td>Metabolized by CYP3A4 and 2C8; an inhibitor of CYP3A4, CYP1A2, CYP2C9, and CYP2D6</td>
<td>Hepatically metabolized by CYP3A4</td>
<td>Hepatically metabolized, 81%-90% renally eliminated</td>
<td>Hepatic metabolism via oxidation, 80% excreted in urine and 20% in feces</td>
<td>Hepatically metabolized by CYP2D6</td>
</tr>
<tr>
<td>Half-life</td>
<td>26-107 days</td>
<td>24 hours</td>
<td>7-22 hours</td>
<td>2-12 hours</td>
<td>2-3 hours</td>
</tr>
<tr>
<td>Adverse drug effects</td>
<td>Pulmonary fibrosis, acute lung injury, thyroid dysfunction, corneal deposits, hepatitis, bradycardia, hypotension, skin discoloration</td>
<td>Nausea, vomiting, diarrhea, QT prolongation</td>
<td>Torsade de pointes, rash, uticaria, nausea, arthralgias, dizziness, headache, fatigue, tremor, heart failure</td>
<td>Bradyarrhythmias, palpitations, headache, torsade de pointes, ventricular arrhythmias</td>
<td>Dysgeusias, sneezing, paresthesia, and nausea</td>
</tr>
<tr>
<td>Dose</td>
<td>Atrial: 150 mg intravenous bolus, then continuous infusion or oral dosing to a total of 6-10 g load followed by 200 mg once daily</td>
<td>400 mg twice daily</td>
<td>200-600 mg orally</td>
<td>Patients &gt;60 kg: 1 mg intravenous over 10 minutes, followed by 3 mg/kg 10 minutes later</td>
<td>Intravenous: 2 mg/kg over 10 minutes, followed by 3 mg/kg 10 minutes later</td>
</tr>
<tr>
<td>FDA-approved indications</td>
<td>Life-threatening ventricular arrhythmias</td>
<td>Approval pending</td>
<td>Paroxysmal atrial fibrillation, atrial flutter, supraventricular tachycardia, life-threatening ventricular tachycardia</td>
<td>Recent-onset atrial fibrillation or atrial flutter</td>
<td>Approval pending</td>
</tr>
</tbody>
</table>
atrial arrhythmias were not included. These and other acutely ill populations require further study to confirm the efficacy and safety of vernakalant in this setting. Patients with QT prolongation at baseline were also excluded from all study populations.11

Efficacy
Vernakalant has shown consistent efficacy in achieving chemical cardioversion of AF. In a phase 2, dose-ranging trial conducted by Roy and colleagues, the highest dose of vernakalant studied (2 mg/kg, followed by 3 mg/kg if necessary) was more effective 30 minutes after infusion than placebo in the cardioversion of recent-onset AF (61% vs 5%, P <.0005).12

In the ACT 1 trial, which was the first phase 3 investigation, the efficacy of vernakalant (3 mg/kg, followed by 2 mg/kg if necessary) in the cardioversion of AF was confirmed in a larger group of patients (n = 336).10 In the primary efficacy analysis, 75 of the 145 vernakalant patients in the short-duration (3 hours to 7 days) AF group converted to sinus rhythm within 90 minutes compared with 3 of the 75 placebo patients (P <.001). Those with long-duration (8–45 days post-onset) AF, however, had less success with chemical cardioversion, and vernakalant failed to demonstrate statistical superiority over placebo (7.9% vs 0%, P = .09). ACT 2 demonstrated the effectiveness of vernakalant in patients developing AF shortly after cardiothoracic surgery (coronary artery bypass grafting or valve replacement), with 47% of patients receiving the study drug converting to sinus rhythm after 90 minutes compared with 14% in the placebo group (P = .0001).13 ACT 3 similarly confirmed the effectiveness of vernakalant in patients with recent-onset AF (3 hours to 7 days), with 51% of patients converting compared with 4% of patients receiving placebo (P <.001).11,14 A pooled analysis of both ACT 1 and ACT 3 patients (n = 390) demonstrated that vernakalant was significantly effective in converting patients with recent-onset AF over placebo.11 Importantly, however, vernakalant was not statistically superior to placebo in converting a cohort of patients with longer duration AF.11

Ongoing trials
Although vernakalant has been recommended for approval by the FDA, additional clinical trials will be important to further define its role in practice. Nevertheless, questions and concerns surrounding the use of vernakalant in the “real world” remain. The most likely application of the intravenous formulation is for recent-onset AF in hospitalized patients necessitating conver-
sion for a perceived hemodynamic benefit or in cases where there is an inability to control ventricular response rate. Patients such as these are likely to be acutely ill from heart failure, myocardial infarction, or other severe illnesses, and although they are the most likely candidates to receive the drug in practice, they were not adequately represented in the clinical trials leading to vernakalant’s approval. Vernakalant also has not been shown to be effective if the duration of AF is greater than 7 days.

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Overall, vernakalant seems to be both efficacious and safe in its ability to convert AF to sinus rhythm; however, the general lack of benefit of rhythm control strategies in major clinical trials may limit widespread use as more practitioners pursue equally viable rate-control options.15,16 While improved safety of newer generation antiarrhythmic agents may lead to additional investigation in the future, vernakalant should at the very least be considered a safer way to convert a patient to sinus rhythm than traditional antiarrhythmic therapy.

References


