Acute Pharmacological Conversion of Atrial Fibrillation to Sinus Rhythm

Is Short-Term Symptomatic Therapy Worth It? A Report From the December 2007 Meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration

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Atrial fibrillation is a common arrhythmia that affects >2 million adults in the United States, with ≈160,000 new cases diagnosed each year. Although many patients are asymptomatic, those with symptoms can experience palpitations, dyspnea, angina, exertional fatigue, and presyncope. The long-term consequences of atrial fibrillation are well described and include increased risk of thromboembolic events that require chronic anticoagulation in most patients.

Reestablishment of sinus rhythm is a key long-term management strategy that would be expected to relieve symptoms, improve hemodynamics, and reduce the risk of thromboembolic complications. Cardioversion is recommended for patients with relatively new-onset atrial fibrillation who are hemodynamically unstable, have uncontrolled rapid ventricular response, or have cardiac ischemia or for acute management of symptoms. Options include synchronized direct current cardioversion, which requires conscious sedation to manage the discomfort of the procedure and is associated with ventricular fibrillation in 0.2% of cases, sinus bradycardia or sinus arrest in 1% of cases, and thromboembolism in 1% of cases not adequately anticoagulated. Pharmacological cardioversion is less effective than direct current cardioversion, but several drugs (dofetilide, flecainide, ibutilide, dofetilide, and propafenone) are currently approved for this indication. These drugs carry risks similar to those of electric cardioversion with the additional concerns of prolonging the QT interval and developing torsade de pointes arrhythmias.

Rates of spontaneous conversion, without the attendant risks of pharmacological or electric conversion, have been reported to be as high as 73% within the first 24 hours after onset, with <50% of patients spontaneously converting after 72 hours of atrial fibrillation. Given this background, 2 new pharmacological agents to convert atrial fibrillation to sinus rhythm in the acute care setting were reviewed by the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration (FDA) on December 11 and 12, 2007. The review of these 2 development programs raised questions about what patients are appropriate for consideration for pharmacological cardioversion, what short-term end points are appropriate, and what is appropriate for consideration for pharmacological cardioversion, what short-term end points are appropriate, and what the risk-to-benefit ratio is.

The drugs were vernakalant (Astellas Pharma US, Deerfield, Ill) and tedisamil (Solvay Pharmaceuticals, Marietta, Ga), and each sponsor pursued similar clinical development strategies to show that its antiarrhythmic drug was safe and effective in converting patients to sinus rhythm. The populations included patients with recent-onset atrial fibrillation who were symptomatic, and the intended indication was to provide a pharmacological alternative for electric cardioversion that would have the benefit of a shortened time in atrial fibrillation (relative to watchful waiting) during 24 hours of observation.

Vernakalant and tedisamil block multiple potassium channels (vernakalant also blocks sodium channels) that regulate atrial conduction and repolarization. The development programs were relatively small, with a total of 1108 patients in the phase 2 and 3 studies for vernakalant and 1470 patients for tedisamil. Both programs enrolled symptomatic patients (palpitations, shortness of breath, chest discomfort) with atrial fibrillation or atrial flutter with a clinical onset of 3 hours to 45 days who were anticoagulated according to current practice guidelines; however, the primary analyses in both programs targeted patients with atrial fibrillation between 3 hours and 7 days. Patients who had class IV heart failure or a myocardial infarction within 30 days were excluded. At presentation to hospital, patients were randomized to active drug or placebo (the option to observe for spontaneous conversion was not evaluated). Investigators were required to avoid elective electric cardioversion and other treatments for 2 hours in the vernakalant program and were discouraged (but not prohibited) from using electric cardioversion within 2.5 hours after initiation of therapy in the tedisamil program.

The primary end points were the percent of patients converting to sinus rhythm (and maintaining for 1 minute) at 90 minutes for vernakalant and conversion to sinus rhythm within 2.5 hours for tedisamil. Both drugs were quite effective in acutely converting patients to sinus rhythm. Vernakalant converted 51% of patients com-
pared with 3.8% on placebo (P<0.001), and this effect was
durable at 24 hours (97% of those who converted with treatment
were in sinus rhythm at 24 hours). Treatment was associated
with a reduced need for electric cardioversion (attempted in 31%
of vernakalant and 69% on placebo). Conversion also was
associated with symptomatic improvement. After 90 minutes,
73% of placebo patients still had symptoms of atrial fibrillation
compared with 50% of those treated with vernakalant.
However, because other treatments were used after the initial
treatment window, most notably electric cardioversion, the
conversion rates to sinus rhythm were very similar between
groups after 24 hours, with 86% of patients randomized to
vernakalant in sinus rhythm compared with 83% of patients on
placebo. Based on similar numbers of patients in sinus rhythm,
66% of patients treated with vernakalant had relief of their
symptoms after 24 hours compared with 70% on placebo.

Tedisamil was studied in gender-specific doses. In men, the
conversion rates were 29% to 53% on drug compared with 6%
to 10% on placebo (P<0.01 and P<0.0001, respectively); in
women, the conversion rates on drug were 18% to 22% compared
with 3% to 5% on placebo (P<0.05 and P<0.0001, respectively).
Similar to vernakalant, acute conversion to sinus
rhythm was durable at 24 hours. However, after 24 hours, 51%
of men treated with tedisamil were in sinus rhythm compared
with 47% on placebo; in women, the rates were 40% and 34%,
respectively. Both drugs reduced the need for electric cardioversion,
particularly in patients with recent-onset atrial fibrillation.

Serious adverse events during the 2-hour infusion period
occurred in 3.3% of vernakalant-treated patients versus 0.9%
of placebo patients. Vernakalant also was associated with
complete atrioventricular block (0.1%), sinus arrest (0.1%),
ventricular fibrillation (0.3%), and heart failure (0.6%) com-
pared with no cases on placebo. Moderate to severe hypoten-
sion occurred in 2.6% of patients on drug and 0.6% on
placebo. Holter monitoring performed for 24 hours revealed
drug-related QT prolongation during the infusion but no cases
of torsade de points. Most concerning was 1 death that occurred
within 1 hour of the initiation of the infusion. Serious adverse
events were reported in 9.7% of tedisamil patients versus 8.7%
of those on placebo. Tedisamil was associated with 5 torsade-
like arrhythmia events in men (3 required electric cardioversion)
and 6 such events in women (2 required electric cardioversion).
There were 2 deaths that were temporally associated with drug
administration, 1 resulting from cardiac arrest and the other from
pulmonary embolism.

There were clear short-term benefits demonstrated in both
programs that included highly statistically significant effects
on initial conversion of atrial fibrillation to sinus rhythm
(with associated symptomatic relief in the vernakalant pro-
amgram) and avoidance of electric cardioversion in those who
responded to the treatment. What was not addressed was
the relative benefit of watchful waiting for spontaneous conver-
sion to occur. It also was not clear how effective the drugs
would have been had the design included a no-treatment run-in phase
followed by randomization of only those patients who had not
already converted on their own. Furthermore, neither program
addressed the larger issues of any benefit of acute pharmacolog-
cal conversion on a reduced risk of thromboembolic or hemor-
rhagic events or need for hospitalization. Thus, the primary
efficacy in these studies was a shortened time in symptomatic
atrial fibrillation (by a few hours) but with significant safety
concerns of increased risk of death, arrhythmias, and hypoten-
sion. On the basis of this overall risk-to-benefit assessment, the
committee was split on recommending approval of vernakalant
(6 for, 2 against). Tedisamil posed additional challenges of a
narrow therapeutic window and the potential for errors with a
complex dosing regimen. These concerns led the committee to
unanimously recommend against approving tedisamil.

Atrial fibrillation is an electrophysiological disorder of cardiac
rhythm that is associated with adverse symptoms, altered cardiac
function, and increased risk of thromboembolic events. Several
trials that compared the 2 long-term treatment strategies of
rhythm versus rate control demonstrated that rate control was
associated with a lower risk of stroke and thromboembolic
events and a lower risk of mortality.5 Thus, the main long-term
benefit of cardioversion is symptomatic relief. Although ver-
nakalant and tedisamil were highly effective in rapidly correct-
ning the underlying cardiac rhythm abnormality, the symptomatic
benefits did not extend beyond a few hours, and any benefit may
have been offset by incompletely characterized harms. These 2
programs emphasize the particularly challenging task of balanc-
ing risks and benefit in drug development programs.

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None.

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