Dronedarone
A New Alternative in Atrial Fibrillation Management

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Atrial Fibrillation (AF) is the most common type of cardiac arrhythmia encountered in clinical practice. It is estimated to affect around 2.5 million people in the US and 250,000 in Canada. As demonstrated in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, rhythm control did not offer any survival benefit in AF over rate control, a finding largely attributable to the pro-arrythmic effects of anti-arrythmic drugs, which negate any survival advantage conferred by maintenance of sinus rhythm.[1] Amiodarone is considered to be the least pro-arrythmic and most efficacious drug among available options, and it is often used to improve functional capacity and quality of life among patients who are symptomatic despite adequate rate control. It is, however, highly toxic with long term effects on almost every organ system, particularly the lungs and the thyroid gland. Because it is lipophilic, it tends to accumulate in lipid-rich body tissues and has an extremely long average-half-life (30 to 55 days).

Dronedarone, a novel anti-arrythmic, has been approved to reduce the risk of cardiovascular hospitalization in the treatment of AF or atrial flutter. Health Canada approved the drug in August 2009 to reduce the risk of cardiovascular hospitalization in patients with a history of, or who currently have, atrial fibrillation. Structurally, dronedarone bears resemblance to amiodarone, with the exception of missing iodine moieties (that likely reduces thyroid and other organ toxicity) and an added methylsulfonamide group (that likely reduces lipophilicity and neurotoxic effects). It retains similar electrophysiologic action in all four anti-arrythmic classes but has a much shorter half-life (1 to 2 days) compared to amiodarone.

Trials of Dronedarone vs. Placebo

The Dronedarone Atrial Fibrillation Study after Electrical Cardioversion (DAFNE) trial was a dose-ranging study designed to demonstrate the optimum daily dose of dronedarone needed to maintain sinus rhythm after cardioversion in patients with persistent AF.[2] Among 199 patients who were randomized to dronedarone, (800, 1200, 1600 mg daily), or to placebo, the time to first AF recurrence was reduced significantly only with the 800 mg dose compared to placebo (60 vs. 5 days, P = 0.001). Pro-arrythmic effects and thyroid, ocular, or pulmonary toxicities were not observed during the sixth month follow-up. Subsequently, investigators utilized a 400 mg b.i.d. dosing regimen in all future trials.

The European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) and American-Australian-African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS) were multinational, phase-three trials with identical protocols, chiefly structured to demonstrate efficacy.[3] Over 1,200 patients with paroxysmal AF and no clinically significant structural heart disease were jointly randomized to dronedarone or placebo. Patients were in a normal sinus rhythm at initiation of the study, and they were followed for one year. Time to arrhythmia recurrence was significantly increased with dronedarone (116 vs. 53 days) compared to placebo, and the recurrence rate at one year was also reduced (64.1% vs. 75.2%, P <0.001). Additionally, among those who had a recurrent arrythmia, ventricular rate was reduced by 12 to 15 beats per minute with dronedarone.

The Anti-arrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA) was not an AF trial, but it sought to evaluate dronedarone therapy among patients with a depressed left ventricular ejection fraction (≤35%) and decompensated heart failure.[4] The study was halted after seven months, because of a twofold excess in morbidity (predominantly cardiovascular) noted in the dronedarone group compared to placebo (25 vs 12, P = 0.03). These results primarily prompted the FDA to include a black box warning in the recent approval against using dronedarone in NYHA Class IV, or recently decompensated Class II to III, heart failure.

A Placebo-controlled, Double-blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg b.i.d. for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter (ATHENA) was a trial designed to address this safety issue and demonstrate the efficacy of dronedarone in the treatment of AF or atrial flutter.[5] Over 4,600 patients with atrial fibrillation and one or more cardiovascular risk factors were included, and rates of first hospitalization, due to cardiovascular events or death, were measured as the primary outcome. Over a 21 month follow-up, the primary outcome was significantly reduced by 24% (31.9% vs. 39.4%, p<0.001). Cardiovascular deaths were reduced by 29% (2.7% vs. 3.9%, p =0.03), chiefly due to a 45% reduction in arrhythmia deaths. All-cause mortality was lower with dronedarone but did not reach statistical significance. No increase in thyroid and lung-related adverse events was noted with dronedarone.

Trials of Dronedarone vs. Amiodarone

The results of the Efficacy & Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation (DIONYSUS)[6] study compared dronedarone to the current standard, amiodarone, for the maintenance of sinus rhythm in over 500 patients with persistent AF.[7] Preliminary results showed that, over seven months, more people had occurrences of the composite primary endpoint (AF recurrence or premature drug discontinuation for intolerance or lack of efficacy) with dronedarone (73.9% vs. 55.3%, P <0.001) compared to amiodarone arm. The hazard ratio at 12 months for dronedarone vs. amiodarone was 1.589 (95% CI 1.275-1.980). Recurrent AF was more prevalent in the dronedarone arm (63.5% vs. 42%). However, dronedarone was safer with fewer adverse events overall, as well as reduced premature study drug discontinuation.

A recent indirect meta-analysis used data from the above trials (except ANDROMEDA) along with four placebo-controlled amiodarone trials to compare the safety and efficacy of dronedarone to that of amiodarone.[8] Patients were twice as likely to remain in sinus rhythm with amiodarone (odds ratio [OR] for AF recurrence 0.49, 95% CI 0.37 to 0.63, P <0.001) compared with dronedarone. However, amiodarone had a less favourable safety profile, with higher rates of adverse events requiring drug discontinuation (OR 1.81, 95% CI 1.33 to 2.46, P <0.001) and a trend toward higher all-cause mortality (OR 1.61, 95% CI 0.97 to 2.68, P =0.07).

New Safety Warning

New information has recently been released by the U.S. FDA regarding liver toxicity.[9] The agency has received several case reports of hepatocellular liver injury and hepatic failure in patients treated with dronedarone, including two post-marketing reports of acute hepatic failure requiring transplantation. Because these reactions are reported spontaneously, it is not known how many patients

have been treated, so the rate of these side effects cannot be determined. The FDA, nonetheless, suggests that healthcare professionals should advise patients to immediately contact them if they experience signs and symptoms of hepatic injury or toxicity (anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching) while taking dronedarone. The FDA has also suggested obtaining periodic hepatic serum enzymes, especially during the first six months of treatment.

Place in Therapy

Thus, a new option now exists for management of AF. It has no known adverse effects on the lungs or the thyroid but does have a black box warning against use in patients with recent heart failure decompensation and a concern about liver toxicity. It is however, the first anti-arrythmic drug that has demonstrated improvement in cardiovascular outcomes (cardiovascular hospitalization or death) in AF.

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