

Dronedarone

- Guidelines for Medical Professionals

The need for new drugs

Atrial Fibrillation (AF) is the most common sustained arrhythmia. Current treatment strategies are divided into rhythm or rate control. Intuitively rhythm control should be superior - preserving physiological function and reducing the risk of clot formation in the atria and thus stroke risk. However clinical trials have failed to demonstrate superiority of rhythm control approaches with the adverse effects of available anti-arrhythmic agents e.g. Sotalol, Amiodarone, potentially negating any benefit conferred by sinus rhythm maintenance. Essentially we need drugs with better risk profiles.

What is Dronedarone?

Dronedarone is a new drug, similar in structure to Amiodarone, in which chemical modifications have shortened the half-life and reduced the risk of thyroid damage (due to an absence of iodine). Its main mechanism of action, like that of Amiodarone and Sotalol, is achieved through the inhibition of potassium channels making heart cells less excitable and thereby making AF less likely.

What are the relative benefits and limitations of Dronedarone?

Dronedarone has been shown to be effective in reducing AF recurrence in patients with paroxysmal and persistent AF. The use of Dronedarone reduces the likelihood of AF by around 25% compared with placebo. It has also been shown to reduce the ventricular response rate by over 10 beats per minute at rest and almost 25 beats per minute during exercise in patients with more persistent

patterns of AF. Importantly it is the only anti-arrhythmic medication demonstrated to improve outcome in AF patients. Specifically in the ATHENA study, Dronedarone reduced the combined risk of cardiovascular hospitalization or all cause-death by 24% in patients with history of AF or Atrial Flutter.

It is well tolerated and does not appear to have adverse effects when compared to placebo. As anticipated and unlike Amiodarone it does not increase thyroid or pulmonary toxicity. In a recently completed study, Dronedarone was found to be less effective than Amiodarone in preventing AF recurrence, but had significantly fewer side effects.

Which AF patients can be prescribed Dronedarone?

Dronedarone may be used to prevent AF recurrence in patients with symptomatic paroxysmal or persistent AF.

Which AF patients should not be prescribed Dronedarone?

Until further information is available, Dronedarone should not be prescribed in patients with heart failure. The ANDROMEDA study which recruited patients with severe heart failure symptoms (but not necessarily in AF) was terminated prematurely because of excess mortality in the Dronedarone arm. Recent use has highlighted increased incidence of heart failure with exposure to the drug, therefore monitoring for symptoms of heart failure should be carried out in all patients using this drug. As Dronedarone is predominantly hepatically metabolised, it should be

avoided in patients with significant liver disorders. There have been rare reports of hepatic failure associated with Dronedarone. Guidance on monitoring and prescribing has been issued by the MHRA, and should be referred to prior to initiating the medication.

What are the side effects and how can these be managed?

Dronedarone is generally well tolerated with no increase in serious adverse effects when compared with placebo. Common side effects are diarrhoea, abdominal discomfort, nausea and vomiting. There is an increased incidence of skin rash, bradycardia and prolonged QT intervals on electrocardiograms although the latter is rare. Most side effects resolve within the first two weeks of starting the drug but in a proportion of patients, Dronedarone will need to be discontinued because of intolerance.

Metabolism and Drug Interactions?

Dronedarone should be taken with meals and is administered at a dose of 400mg twice daily. It has a half-life of around 30 hours and is metabolized by cytochrome CYP3A4 and is itself a moderate inhibitor of the enzyme.

Therefore, potent inhibitors of CYP3A4 such as ketoconazole, macrolide antibiotics, cyclosporine and protease inhibitors will increase plasma Dronedarone concentrations. On the other hand, Dronedarone may raise the blood concentration of drugs metabolized by CYP3A4, such as verapamil and simvastatin. It can also increase digoxin concentrations. However, in the major clinical trials, commonly used cardiac medications were allowed, and did not increase adverse effects. Dronedarone should not be taken together with grapefruit

juice or certain herbal products such as St. John's Wort.

Dronedarone may increase serum creatinine by decreasing its renal tubular excretion without affecting kidney function.

Currently there is not enough safety evidence to allow its use in pregnancy or during breast-feeding.

Patients should be warned to consult their physicians if they develop symptoms of worsening heart failure.

Conclusions

Dronedarone is a much-anticipated drug. It has the advantage of having fewer and in general less severe side effects than Amiodarone but is demonstrably not so effective. Its cautious introduction into clinical practice is to be welcomed whilst accepting that other drugs will retain important roles. As the options for AF management continue to increase the need for expert specialist advice to help patients to make properly informed decisions will become more pressing.

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