

Dronedarone

The need for new drugs

Atrial Fibrillation (AF) is the most common sustained arrhythmia. Current treatment strategies are divided into rhythm or rate control and one would think that rhythm control (that is maintenance of normal sinus rhythm) should be superior. However clinical trials have failed to demonstrate superiority of rhythm control approaches, in fact there can be adverse side effects from currently available anti-arrhythmic medications such as Sotalol and Amiodarone. Potentially these can be more unpleasant or harmful than any benefit gained by maintaining sinus rhythm. So, essentially we need anti-arrhythmic drugs with better 'risk profiles' that is, they improve a patient's symptoms without having many or any side effects or risks linked to them.

What is Dronedarone?

Dronedarone is a new drug, similar in structure to Amiodarone, in which chemical modifications have shortened the half-life of this drug (the time it remains in the body still active), and reduces the risk of thyroid damage (this has been achieved by omitting 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 the recurrence of AF in patients with paroxysmal (episodes which come and go) and persistent (AF which will not revert to sinus rhythm without medical or electrical cardioversion) AF.

The use of Dronedarone has been shown in trials to reduce the likelihood of AF by around 25% compared to a placebo. It has also been shown to reduce the ventricular response rate by over 10 beats/minute at rest and almost 25 beats/minute during exercise in patients with more persistent patterns of AF.

Importantly it is the only anti-arrhythmic medication demonstrated to improve long term cardiac health in AF patients. This was shown in the ATHENA study, where Dronedarone reduced the combined risk of cardiovascular hospitalization or all cause-death by 24% in patients with a history of Atrial Fibrillation 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 the risk of related health problems in the thyroid or pulmonary areas due to toxicity. A recently completed study showed that while Dronedarone was less effective than Amiodarone in preventing AF recurrence, it 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?

An increased incidence of heart failure has been seen with exposure to this drug, therefore Dronedarone should not be prescribed in patients with heart failure and monitoring should be carried out in all those using it.

Dronedaronone should also be avoided in patients with significant liver disorders and there have been recent rare reports of hepatic (liver) failure associated with Dronedaronone. Guidance on monitoring has been issued by the Medicines and Healthcare products Regulatory Agency.

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

Dronedaronone is generally well tolerated with no increase in serious adverse effects when compared with placebo.

The most common side effects noted are: diarrhoea, abdominal discomfort, nausea and vomiting. There is an increased incidence of skin rash, bradycardia and prolonged QT intervals on electrocardiograms (ECGs) although the latter is rare. Most side effects resolve within the first two weeks of starting the drug, but it is thought that in a proportion of patients, Dronedaronone will need to be discontinued because of intolerance.

What other information needs to be passed on to GPs and patients?

Currently, Dronedaronone will only be available for prescription through specialist teams, not through a GP.

Dronedaronone should be taken with meals and is administered at a dose of 400mg twice daily. It has a half-life of around 30 hours.

Dronedaronone may raise the blood concentration of drugs such as Verapamil and Simvastatin. So this may need to be closely monitored. It can also increase Digoxin concentrations. However, in the major clinical trials, commonly used cardiac medications were allowed, and these did not increase adverse effects. Dronedaronone should not be taken together with grapefruit juice or certain herbal products such as St. John's Wort.

Dronedaronone has not been shown to affect kidney function.

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

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

Conclusions

Dronedaronone is a much-anticipated drug. It has the advantage of having fewer and in general less severe side effects than Amiodaronone but is demonstrably not so effective. Its cautious introduction into clinical practice is to be welcomed, whilst accepting that other drugs will still have 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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