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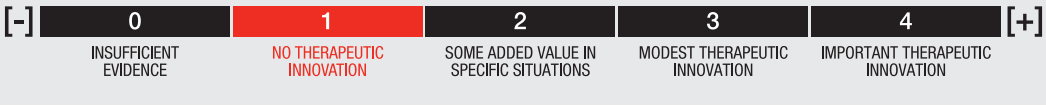
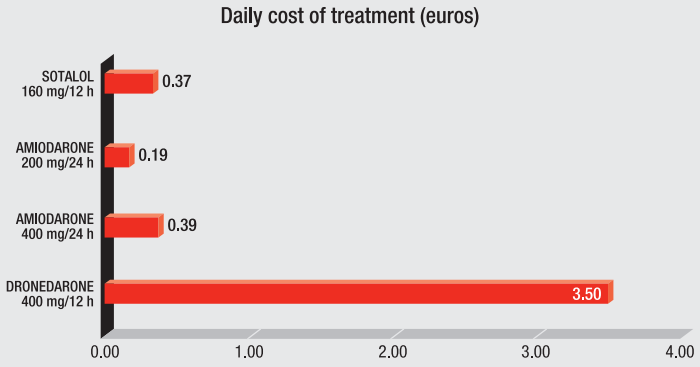
Dronedarone▲ (Multaq®) for non-permanent atrial fibrillation

Lower efficacy than amiodarone and a questionable safety profile





- Dronedarone is less effective than amiodarone in preventing recurrent episodes of atrial fibrillation.
- Its safety profile is far from established. An increase in mortality in patients with heart failure and a warning of hepatic abnormalities have been published.
- Although it does not produce thyroid disorders like amiodarone, on a whole it has not been shown to be more effective.
- The potential for interactions is even more complex than amiodarone.
- In addition to this data, the price of dronedarone is ten times higher than that of amiodarone.

Therapeutic indications[1]

Dronedarone is indicated in adult clinically stable patients with a history of, or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate.

Mechanism of action and pharmacokinetics[1]

This antiarrhythmic agent is similar to amiodarone. It blocks potassium channels prolonging the heart's action potential and refractory periods (Class III). It also inhibits sodium (Class Ib) and calcium channels (Class IV) and is a non-competitive blocker of adrenergic sympathetic activity (Class II).

Taken with food, peak plasma concentrations of dronedarone and its active metabolite, N-debutyl are reached after 3-6 hours. Given the first pass effect, the bioavailability is about 15%. A steady state is reached in 4-8 days. It is extensively metabolized, mainly through CYP3A4. It is excreted mainly in its metabolite form, 6% in urine and 84% in feces. The elimination half-life is 25-30 hours. In women, serum levels are 1.3 to 1.9 times higher than in men.

Use antiarrhythmic agents that are supported by more experience in their use

Posology and administration[1]

One 400 mg tablet should be taken at breakfast and another one at dinner. In case a dose is missed, then the next dose should be taken at the next regular hour. The dose should not be doubled.

Clinical efficacy[1,2]

The only trial comparing the efficacy with another antiarrhythmic agent is the DIONYSOS[8] which compared dronedarone 400 mg twice daily with amiodarone (600 mg once a day for 28 days, followed by 200 mg daily for 6 months). The trial included 504 patients with AF in which cardioversion and antiarrhythmic treatment was indicated. The primary endpoint was time up to the first AF recurrence or premature suspension of the drug due to intolerance or lack of efficacy.

Dronedarone was inferior to amiodarone, with an incidence of the primary outcome of 75% vs 59%, respectively (HR = 1.59; CI95%, 1.28-1.98). Recurrence of AF was 63.5% vs 42% for dronedarone and amio-

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.

darone respectively. Recurrence of AF after electric cardioversion ocurred in 36.5% of the cases in the dronedarone group compared to 24.3% in the amiodarone group. The trial had a median follow up of 7 months.

Safety[1,2]

A warning was issued concerning the use of dronedarone and severe hepatic disorders, including cases of fulminant hepatic failure that required liver transplants. Liver function tests should be carried out before initiating treatment with dronedarone and monthly for the first 6 months, then after 9 and 12 months and finally periodically. Should an increment in ALT ≥ 3 be detected then treatment with this drug should be discontinued[10].

The ANDROMEDA trial[7] carried out in patients with heart failure was stopped prematurely due to an excess in mortality attributed to worsening heart failure after two months of treament in the dronedarone group (25 deaths of 310 patients) compared to the placebo group (12 deaths of 317 patients).

The DIONYSOS trial[8] showed no significant differences between dronedarone and amiodarone with regard to the composite endpoint including safety (first event affecting thyroid gland, lungs, nervous system, skin, eye, gastrointestinal system or premature suspension of treatment due to an adverse effect, HR = 0.80 (CI95%, 0.60-1.07). The incidence of specific adverse events affecting the thyroid gland or nervous system was lower for dronedarone when compared to amiodarone (thyroid: 0.8% with dronedarone vs 5.9% amiodarone; nervous system: dronedarone, 1.2% vs amiodarone, 6.7%). However, the incidence of gastrointestinal adverse effects was greater in the case of dronedarone when compared to amiodarone (12.9% vs 5.1% respectively).

Unlike amiodarone, no cases of adverse effects affecting the lungs have been reported in those patients under dronedarone. However, pulmonary affectation occurs over a prolonged period of time, and no long-term data is available as yet with regard to dronedarone.

Adverse reactions

Treatment withdrawal due to adverse effects occured in 11.8% of the cases under dronedarone compared to 7.7% under placebo. The most frequent adverse effects during the clinical trials include: diarrhoea, asthenia, nausea and vomiting, rhythm and heart rate disorders (the most frequent bradycardia), modifications in renal parameters, rash, skin eruptions or exanthemas, and changes in the EKG (prolonged QT interval and QTc).

Contraindications[1]

· Second or third degree atrio-ventricular block or sick sinus syndrome (except when employed with a pacemaker).
· Bradicardia <50 bpm.
· Hemodynamic instability including heart failure at rest or minimal activity. Precaution should be taken in stable patients with class III heart failure or LVEF<35%.
· Use of potent inhibitors of the CYP3A4 is contraindicated.
· Drugs that can induce torsade de pointes syndrome such as phenothiazines, tricyclic antidepressants, macrolides, and class I and II antiarrhythmic agents should not be given.
· Dronedarone can increase the QT interval and EKG monitoring should be performed. Should a prolongation of the Bazett´s QTc interval occur of ≥ 500 ms then treatment should be discontinued.
· Severe liver failure or severe renal failure (ClCr < 30 mL/min).
· Hypersensitivity to the active substance or excipients or galactose intolerance.

Precautions[1]

An increase in serum creatin concentrations has been reported and therefore concentrations should be monitored after one week of treatment. Should there exist an increase in creatin concentrations, this increment should be taken as the new baseline value. Before initiating treament any alterations in potassium or magnesium concentrations should be corrected.

Interactions[1]

The profile of interactions with the use of dronedarone is even more complex than amiodarone[2]. Please consult the section on contraindications.

Moderate inhibitors of CYP3A4 can increase serum concentrations of dronedarone. Moreover, verapamil and diltiazem can potentiate bradycardia, thus combined use with dronedarone should be carried out with precaution.

Grapefruit juice should be avoided as it increases the levels of dronedarone. Inducers of CYP3A4 reduce dronedarone levels by 80% and therefore their combination is not recommended.

Dronedarone inhibits CYP3A4, CYP2D6 and P-glycoprotein, and therefore can affect those drugs that are substrates of these coenzymes. Serum concentrations of simvastatin, lovastatin and atorvastatin can increase. The interaction with fluvastatin and rosuvastatin has not been studied. Lower doses of statin therapy should be considered at the onset of treament and close monitoring for clinical signs of muscle toxicity is recommended.

Dronedarone increases digoxin levels, and therefore the dose of the latter should be reduced by 50%, and measurements of serum concentrations, clinical and EKG monitoring should be carried out. A synergic effect exists on the heart rate and on atrio-ventricular conduction. Serum concentrations of tacrolimus and sirolimus can increase and therefore monitoring is recommended.

Beta blockers to be employed in combined use with dronedarone should be initiated at low doses and adjustments can be made once EKG abnormalities have been ruled out.

Use in special situations[1]

Pregnancy: not recommended given lack of data. **Nursing mothers:** animal studies have shown excretion in breast milk. **Children:** not recommended in patients under 18 years of age. **Elderly patients:** no dose adjustments are considered necessary. **Hepatic impairment:** this drug is contraindicated in patients with severe liver failure given the lack of data available. No dose adjustments are required in cases of mild and moderate hepatic impairment. **Renal impairment:** contraindicated in severe renal impairment. No dose adjustments are necessary in other patients with renal failure.

Place in therapeutics

In patients suffering from atrial fibrillation and with hemodynamic compromise due to myocardial ischemia, or with severe symptoms caused by a rapid ventricular response, electric cardioversion should be considered. Sotalol or amiodrone should be considered the recommended management option to prevent recurrence of AF in symptomatic patients.

Dronedarone is less effective than amiodarone in the prevention of recurrences of AF and has not proven to be safer. Unlike amiodarone, dronedarone is contraindicated in patients with heart failure presenting symptoms at rest or minimal activity. It also requires monitoring of liver function and there is no data on its long-term efficacy and safety profile. For all these reasons, patients with AF should continue to use the first-line management options employed upto now.

Presentations

Multaq® 400 mg 60 tablets. Sanofi Aventis Ltd. (104.9 €). Prescription medicine only.

References

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