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A review on dronedarone: Pharmacological, pharmacodynamic and pharmacokinetic profile

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ABSTRACT

Dronedarone, a benzofuran containing chemical compound, is a derivative of amiodarone which is classified as a Class III antiarrhythmic agent. It is prescribed to the cardiovascular patients who have paroxysmal or persistent atrial fibrillation to lower the chances of hospitalization. Amiodarone, sotalol, procainamide dofetilide, quinidine, ibutilide, flecainide, and propafenone are the other useful medicinal products used to treat atrial fibrillation or cardiac arrhythmia. Dronedarone was approved for clinical use in atrial fibrillation by the Food and Drug Administration in 2009. The generic name for dronedarone is Multaq (Sanofi Aventis). This article briefly highlights the important pharmacological, pharmacodynamic and pharmacokinetic properties of dronedarone.

1. Introduction

Dronedarone is a structural analog of antiarrhythmic drug amiodarone. It belongs to Class III of antiarrhythmic drugs. Amiodarone is a popular antiarrhythmic agent but potential toxicity associated with this drug limits its clinical usefulness. Its regular use may cause several diseases such as thyroid disease, pulmonary fibrosis and also liver disease which might be due to the presence of high iodine content in it. Dronedarone is relatively a new drug which can lower the chances of hospitalization in patients having cardiovascular diseases especially those with paroxysmal or persistent atrial fibrillation (AF), having sinus rhythm (SR), or patients likely to be cardioverted[1]. It was given approval for clinical use in AF by the Food and Drug Administration in 2009.

AF is considered as one of the commonest forms of cardiac arrhythmia. Some of the commonly associated risk factors for AF are heart failure, pericarditis, congential heart defects and coronary artery disease, *etc*. The main therapeutic goals to be achieved in the management of AF include: ventricular rate control, prevention of thromboembolic events and rhythm control *i.e*., to restore the SR[2]. To control the ventricular rate, some agents which typically block the atrioventricular node are used. Commonly prescribed agents to control rate include calcium channel blockers (diltiazem and verapamil), β-blockers and digoxin, *etc*. Whereas, in rhythm control or restoration of SR, Class Ic and III anti-arrhythmic agents are employed. The currently available Class Ic and III are reported to have unpredictable efficacy and limiting safety profile[3].

Multaq is a generic name for dronedarone marketed by a multinational Sanofi Aventis Company, Paris, France. Chemically, dronedarone is a non-iodine containing benzofuran analog of antiarrhythmic drug amiodarone which is proven effective for pharmacologic cardioversion[4,5]. In clinical trials, dronedarone was found to be better than amiodarone in terms of having a relatively quicker and short half-life, reduced lipophilicity, and negligible non-cardiovascular toxicity. It is preferred for the long term therapy of AF or flutter in comparison to any other antiarrhythmic drug because of its safety and efficacy. Dronedarone has been proved to be quite safer and effective drug in controlling the SR and decreasing the ventricular pro-arrhythmias.

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Dronedarone is considered to be the best choice for control of rhythm in AF patients having no record of heart disease, coronary artery disease and hypertension without left ventricular hypertrophy[6–9].

2. Chemistry

The chemical name of dronedarone is *N*-(2-Butyl-3-(*p*-(3-(dibutylamino)propoxy)benzoyl)-5-benzofuranyl)methane-sulfonamide (Figure 1). Its molecular formula is $C_{31}H_{44}N_2O_5S$ with molecular mass of 556.758 g/mol.

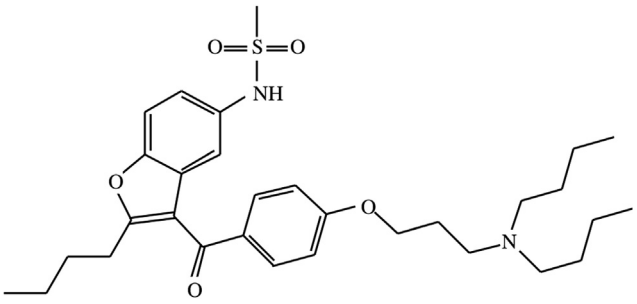

Figure 1. Chemical structure of dronedarone.

Dronedarone is a benzofuran containing heterocyclic compound and is a structural analog of amiodarone, but with slight structural modifications where the iodine group is replaced by a methane-sulfonyl group. The intention behind the replacement of iodine group is to reduce the risk of non-target organ adverse effects caused by amiodarone therapy. The substitution of iodine with the methane-sulfonyl group reduces the lipophilicity and thus decreases the risks of neurotoxicity and shortens the dronedarone's half life significantly[10–14]. Dronedarone is crystalline in nature with melting point of 149–153 °C. It also seems to display activity in each of the 4 Vaughan-Williams antiarrhythmic classes[15–17].

3. Pharmacology

3.1. Mechanism of action

Dronedarone is a Class III antiarrhythmic drug with characteristics of all four Vaughan-Williams. Very similar to Class I drugs, it shows rate-dependent inhibition of the rapid Na^+ current, inhibits α and β-adrenergic receptors like Class II agents, exhibits blockade of K^+ outward currents as the main mechanism of action of Class III, and effectively block slow Ca^{2+} inward currents (Class IV)[18,19]. Class I and III effects provide an insight into the mechanisms that induce rhythm control by increasing refractory periods and decelerating cardiac conduction. Because of its balanced inhibition of multiple outward currents, it may reduce the transmural dispersion of repolarization, that prevents significant proarrhythmic effects associated with other antiarrhythmic drugs[20]. Furthermore, in comparison to pure potassium channel blockers, dronedarone can increase duration of action potential and effective refractory period without causing reverse use-dependency[20,21]. Beside this, Class II and IV effects of dronedarone can lead to rate control properties along with anti-adrenergic (Class II) and blood pressure lowering (Class IV) effects[22,23].

The electrophysiological effects of dronedarone in animal models are found to be similar to the prototype drug, amiodarone. Similar to amiodarone prototype, oral dronedarone also exhibits an increase in the PR interval in a dose-dependent manner, as well as moderate prolongation of the QT interval corrected for rate (QTc)[1,5,8]. Dronedarone also prolongs the RR and QT intervals[14–17,24–26].

3.2. Indication

Dronedarone hydrochloride is used to lower the hospitalization chances for cardiovascular events in patients with paroxysmal or persistent AF who have had a recent episode of AF/atrial flutter (AFL) and who have associated cardiovascular risk factors (*i.e.*, older than 70 years of age, hypertension, prior cerebrovascular accident, diabetes, left atrial diameter of 50 mm or greater, left ventricular ejection fraction of less than 40%). The drug is indicated in patients who are in SR or who will undergo cardioversion[24,25,27].

3.3. Posology

The maintenance dose is 1 tablet (400 mg) two times a day *i.e.*, morning and evening with meals. All antiarrhythmic drugs of Class I, III and/or strong CYP3A4 inhibitors should be discontinued before initiating therapy with dronedarone.

3.4. Adverse events

Listed below are some of the common side effects of dronedarone[1,24,28–31].

Use of dronedarone will lead to some gastrointestinal (GI) effects including stomach pain, indigestion, nausea, vomiting, heartburn, diarrhea, loss of appetite, loss of taste (rare), *etc*. Some general side effects such as feeling of weakness or tiredness, loss of strength may also occur. Cardiac disfunctions such as slow or irregular heart beats, bradycardia, heart failure (rare); respiratory disorders including non-productive cough, difficulty in breathing, interstitial lung disease; skin and subcutaneous tissue side effects such as cracked, dry skin, itching skin, rashes encrusted, scaly and oozing, eczema, dermatitis, redness or discoloration of skin, photosensitivity reaction (rare) would also appear during dronedarone usage (Table 1).

Laboratory data/electrocardiograph parameter changes including increased serum creatinine, bilirubin and hepatic enzymes, QTc prolongation (28%) can also occur.

3.5. Overdose

The overdose of dronedarone can be very toxic. It is not known whether dialysis (hemodialysis, peritoneal dialysis, or hemofiltration) can remove dronedarone and/or its metabolites from the blood. Currently, specific antidote is not available for the dronedarone toxicity either due to accidental or intentional overdosing. In case of overdose, supportive treatment is provided which aimed towards alleviating symptoms.

3.6. Contraindications

Dronedarone is contraindicated in the following conditions[10,25,32]: (a) atrio-ventricular block (2nd or 3rd degree), sick sinus syndrome (except when used together with well operational pacemaker); (b) bradycardia with less than fifty beats per