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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.

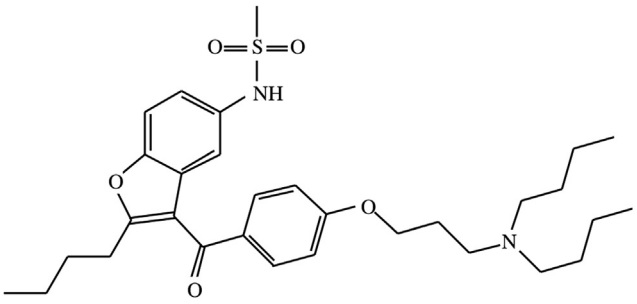

Figure 1. Chemical structure of dronedarone.

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

Table 1
Some common side effects of dronedarone.

Frequency	Side effects
Very common (≥ 1/10)	Cardiac disorders: Congestive heart failure and QT interval prolonged. Blood creatinine increased
Common (≥ 1/100 to < 1/10)	Asthma, fatigue, rashes, liver function abnormalities, diarrheas, vomiting nausea, abdominal pain, dyspepsia
Rare (≥ 1/10000 to < 1/1000)	Anaphylactic reactions including angioedema, ageusia, leukocytoclastic vasculitis, hepatocellular liver injury including life-threatening acute liver failure.

minute (< 50 bpm); (c) patients who are taking strong CYP3A inhibitors *e.g.* azithromycin, telithromycin, clarithromycin, erythromycin, cobicistat, chloramphenicol, clotrimazole, cyclosporine, cimetidine, diltiazem, fluoxetine, fluconazole, ketoconazole, miconazole, oxiconazole, itraconazole, posaconazole, voriconazole, fluvoaxamine, gestodene, indinavir, nelfinavir, ritonavir, saquinavir, ritonavir, valproic acid, *etc.*; (d) patients who are using herbal products and other drugs which increase the QT interval and drugs like tricyclic antidepressants, bepridil, cisapride, phenothiazines, terfenadine and some oral macrolide which might induce Torsades de Pointes; (e) patients with the highest QTc Bazett interval (≥ 500 ms); (f) pregnancy and lactating women; (g) patients with unstable hemodynamic conditions; (h) patients with a history of left ventricular systolic dysfunction or having a heart failure; (i) patients who reported to have lung and liver toxicity due to use of amiodarone; (j) severe case of liver dysfunction or any type of hepatic toxicity; (k) kidney dysfunction or any type of severe renal impairment with low creatinine clearance (CrCl < 30 mL/min).

3.7. Warnings and precautions

Severe liver injury as well as acute liver failure was observed in dronedarone (Multaq) treated patients in the post-marketing surveillance[32,33].

There is a strong possibility of hypomagnesemia or hypokalemia with concurrent use of potassium-depleting diuretics with dronedarone. We should ascertain that level of serum magnesium and potassium concentrations are within normal limits before initiating the therapy and maintained within normal range during the duration of the therapy of dronedarone[32,33].

3.8. Drug interaction

Dronedarone interacts with many drugs (so need to avoid concurrent use) such as antiarrhythmic drugs, digoxin (we should discontinue or divide the dose of digoxin and monitor during the treatment), beta-blockers, calcium channel blockers, HMG-CoA reductase inhibitors, monoamine oxidase inhibitors, lactose, juice of grapefruit, CYP3A substrates with low therapeutic index like tacrolimus and sirolimus, and CYP3A inducers *viz*. carbamazepine, phenytoin, phenobarbital, rifampicin, potent CYP3A4 inhibitors like azithromycin, telithromycin, clarithromycin, erythromycin, cobicistat, chloramphenicol, clotrimazole, cyclosporine, cimetidine, diltiazem, fluoxetine, fluconazole, ketoconazole, miconazole, oxiconazole, itraconazole, posaconazole, voriconazole, fluvoxamine, gestodene, indinavir, nelfinavir, ritonavir, saquinavir, ritonavir, valproic acid, *etc*.[24–26,34,35].

4. Pharmacokinetics and pharmacodynamics

4.1. Pharmacodynamic properties

Dronedarone decreases the heart rate and increases the Wenckebach cycle length and AH-, PQ-, QT-intervals. It has no noticeable effect but weakly amplify the QTc-intervals, further, it does not change HV- and QRS intervals. It also augments the effective refractory periods of the atrium, atrio-ventricular node, while cause little prolongation in the ventricular effective refractory periods[1,10].

Dronedarone decreases myocardial oxygen consumption, reduces arterial blood pressure and contractility of myocardium with no effect in left ventricular output volume.

It has vaso-dilatory properties and also been reported to show indirect anti-adrenergic effects with partial antagonism of stimulation of adrenergic system.

4.2. Pharmacokinetic properties

Dronedarone is less lipophilic as compared to the amiodarone. It has very less volume of distribution. The elimination half-life ($t_{1/2}$) of dronedarone is quite shorter (13–19 h) in contrast to half-life of amiodarone which is several weeks. The dose of dronedarone may be less complex than amiodarone due to the pharmacokinetic profile[14,36–38] (Table 2).

4.2.1. Absorption

The absorption is nearly 70%–94% which increases significantly in presence of food. The bioavailability (absolute) in absence of food is reported as low which is nearly 4% and this is mainly due to pre-systemic first pass metabolism. The presence of fatty meal increases the bioavailability of dronedarone to nearly about 15%, therefore, it is recommended to be taken with food. T_{max} of dronedarone and its active metabolite *N*-debutyl is reported as 3–6 h and steady-state concentrations are achieved in 4–8 days upon oral administration after meal. When dronedarone is administered repeatedly in a dose of 400 mg twice daily, it shows mean accumulation ratio from 2.6 to 4.5. The maximal steady-state concentration is found to be 84–167 ng/mL. The area under the curve is 650–1 030 ng·h/mL. The steady state C_{max} and contact of its active metabolite of *N*-debutyl is reported to be similar. The pharmacokinetic properties of both dronedarone and its metabolite "*N*-debutyl"' show a slight deviation from the dose proportionality: doubling the dose results in nearly 2.5–3.0 times increase in C_{max} and area under the curve[14,49].

4.2.2. Distribution

Dronedarone and its main active metabolite *N*-debutyl binds strongly to the plasma proteins (> 98%), mostly to the albumin

Table 2
Comparison of amiodarone and dronedarone[39–45].

Drug	Vaughan Williams	Indication	Onset of action	Half life	Protein binding and metabolism	Route of elimination
Dronedarone	All four classes of Vaughan Williams	To decrease the chances of hospitalization in case of sudden/ continual AF/AFL with current episode of AF/AFL & related CV risk factors[41].	4–8 h	13–19 h	> 98% by CYP3A and CYP2D6[47]	~ renal (6%) and feces (84%)[48]
Amiodarone	All I–IV classes, but predominantly Class III	Paroxysmal supra-ventricular tachycardia (paroxysmal SVT); Recurrent ventricular fibrillation; Supra-ventricular arrhythmias; Unstable ventricular tachycardia; Recurrent supra-ventricular tachycardia; Management of acute AF and long term treatment to prevent recurrence of AF[46]	Few days to weeks (1–3)	40–55 days	> 96%, by CYP3A4 and CYP2C8[38]	Metabolized by liver & biliary excretion[24]

and is not saturable. The volume of distribution at steady state ranges from 1 200 to 1 400 L after intravenous administration. Dronedarone is widely distributed in kidneys, liver, lungs, myocardium and also crosses the blood-brain and placental barriers[48].

4.2.3. Biotransformation

Dronedarone is metabolized by the cytochrome (CYP) P450 CYP3A4 isoenzyme (> 84%) to its active metabolite *N*-debutyl and the inactive propanoic acid metabolite. Its active metabolite is 3–10 folds less potent than dronedarone. The initial metabolic pathway involves *N*-debutylation which results in the formation of an active *N*-debutyl metabolite. The active metabolite further undergoes oxidative deamination and direct oxidation to form an inactive propionic acid metabolite. The metabolite through a series of biotransformation also yields more than 30 unidentified metabolites. The main active metabolite *N*-debutyl possesses 1/10 to 1/3 pharmacodynamic activity in comparison to parent drug[46,50].

4.2.4. Elimination

The elimination half-life of dronedarone varies from 13 to 19 h. It is mainly excreted in the feces (84%), while 6% is excreted in the urine. It is reported in the mass balance study of dronedarone that orally administered dronedarone (^{14}C-labeled) approximately 6% and 84% of the labeled dose was excreted in urine and in faeces respectively, chiefly as active metabolites. This drug is not excreted in urine as unchanged compound. Dronedarone and its active metabolite *N*-debutyl dronedarone is reported to be fewer than 15% of the resultant radioactivity in the plasma. The plasma clearance (Cl) of dronedarone is approximately 130–150 L/h after IV administration[47].

4.2.5. Special populations

There is no difference in the pharmacokinetic profile of dronedarone among healthy subjects and AF patients[14]. The female patients have shown higher plasma exposure of dronedarone as compared with male patients. The plasma exposure of dronedarone is approximate1y 1.3-fold greater in females as compared to their counterparts. With respect to the body weight, the plasma exposure of drug is 1.4 times higher among the patients having body weight 60 kg in comparison to the patients with 60–100 kg of body weight. The pharmacokinetics of dronedarone does not differ significantly among patients having heart failure and kidney diseases history. The dosage adjustment is not required in the patients having moderate liver dysfunction. Dronedarone is contraindicated in the patients suffering from severe hepatic impairment since severe hepatocellular liver damage and sometime life-threatening acute liver failure has been reported in patients treated with dronedarone in the post-marketing surveillance studies. In patients suffering from moderate hepatic impairment, it was observed that the steady-state exposure increased by 1.3-folds for dronedarone and decreased from 1.6 to 1.9-folds for its active metabolite[32].

5. Preclinical safety data

In preclinical safety study of dronedarone, it is reported that dronedarone had no genotoxic property after evaluation of four *in vitro* tests and *in vivo* micronucleus test in mice[6,12,28–30,51–54].

5.1. ATHENA

In ATHENA study, Connolly *et al*. conducted a placebo controlled, double blind trial[6].

They included total 4 628 patients with age over 75 years in the study. All patients were checked if they had either persistent or paroxysmal AF or AFL and at least one added risk factor for cardiovascular events. These patients were randomly received either placebo or dronedarone 400 mg twice daily. All these patients were treated for the duration of minimum twelve months. In this study, the primary end point was death due to any cause or cardiovascular hospitalization, while secondary end points were cardiovascular hospitalization or cardiovascular death.

There was a statistically significant reduction in the dronedarone group for cardiovascular death, total strokes, transient ischemic attack, and the composite of stroke.

5.2. EURIDIS and ADONIS

A double blind, randomized trial was conducted by Singh *et al*., total 828 patients included[55]. These patients were randomized to receive either placebo or dronedarone 400 mg two times daily. In this study, a primary end point was time to recurrence of AF, while secondary end points were symptoms associated with AF and the mean ventricular rate

during the recurrence of AF. It was observed that, heart rate was decreased and QT interval was prolonged in the dronedarone treated group.

5.3. DAFNE

A double-blind, randomized placebo-controlled, dose-ranging study of the dronedarone was carried out for the prevention of AF[28]. This study used three different doses of dronedarone *viz*. 400 mg, 600 mg, and 800 mg, two times daily in 270 patients with AF contrast to placebo for the management of SR following electrical cardioversion. The treatment was continued for the duration of 6 months. The dronedarone at a dose of 400 mg twice daily as compared to placebo delayed the AF recurrence. This study demonstrated that dronedarone at a dose of 400 mg orally twice daily regimen had more efficacy and it was considered to be adequately safe to continue to more clinical trials.

5.4. ERATO

A double-blind, randomized, placebo-controlled trial was carried out to evaluate the efficacy and safety of dronedarone for the control of ventricular rate during AF (ERATO)[30]. A total of 174 patients with symptomatic permanent AF were included in the study. The efficacy of dronedarone 400 mg two times daily for the duration of 6 months in controlling ventricular rate in these patients was evaluated. It was noted that dronedarone significantly decreased the ventricular rate and this effect was sustained during the course of study *i.e*., six months.

5.5. ANDROMEDA

The evaluation of dronedarone in moderate-to-severe congestive heart failure for morbidity decrease (ANDROMEDA) is a randomized double-blind, placebo-controlled trial based study in 627 patients hospitalized for heart failure[56]. The study was carried out for the evaluation of the efficacy of dronedarone at a dose of 400 mg two times daily on the risk of hospitalizations for worsening heart failure or mortality.

It was observed that only one fourth of the study population had atrial flutter/AF at randomization. There was a total of ten deaths due to worsening heart failure in the dronedarone treated group while only two deaths were seen in the placebo group. The trial was early terminated due to this outcome and observations. The exact mechanism which leads to worsening of heart failure in dronedarone treated group is unknown and need to be investigated. One of the possible mechanisms of this toxicity which was caused by increase in the serum creatinine level could be due to the withdrawal of angiotensin-converting enzyme inhibitors in dronedarone patients.

6. Conclusions

The dronedarone has been observed to be more efficacious in reducing the incidence of recurrence of AF. The dronedarone is also found to be better tolerated than amiodarone. It is shown to have a low pro-arrhythmic risk and this is the first anti-arrhythmic drug which has been found to reduce risk factor for recurrent AF, cardiovascular mortality and hospitalization in patients who are clinically stable along. Therefore, dronedarone as an anti-arrhythmic drug, has been recommended as drug of choice for the maintenance of SR in the clinically stable patients. Many studies have also proved that dronedarone is a potent anti-arrhythmic drug.

In the ADONIS and EURIDIS studies, the efficacy of dronedarone in maintaining SR was evaluated. The dronedarone significantly reduced the risk of recurrence of AF as compared to placebo. The capacity of dronedarone to control ventricular rate in permanent AF was evaluated in the ERATO study. The recurrences of AF were demonstrated in the DIONYSOS study. Additionally, it was also demonstrated in the ATHENA study that dronedarone can greatly reduce the death and cardiovascular hospitalization (24%) in patients due to SR. On the other hand, the efficacy of dronedarone in patients with recent decompensated heart failure was also evaluated in the ANDROMEDA study. The use of dronedarone in patients with chronic AF was evaluated in the PALLAS. These studies were permanently terminated due to a tendency of higher risk of cardiovascular events.

Conflict of interest statement

The authors report no conflict of interest.

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