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Review article

Dronedarone—current status in management of atrial fibrillation

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ABSTRACT

Atrial fibrillation (AF) is the most common of the serious cardiac rhythm disturbances and is responsible for substantial morbidity and mortality. Available drug therapy for AF has modest efficacy and is associated with the risk of life-threatening pro-arrhythmic complications.

Dronedarone is a newer therapeutic agent with a structural resemblance to amiodarone and a better side effect profile. It is a multichannel blocker with antiadrenergic properties and has been evaluated in both rate and rhythm control strategies in the management of AF. In this review, we discuss the current role of dronedarone in the contemporary management of AF.

Introduction

Atrial fibrillation (AF) is a common arrhythmia in clinical practice contributing to significant cardiovascular morbidity and mortality. The prevalence of AF increases with age and adversely impacts the healthcare resources. Major trials have shown the adequacy of rate-control in the management of AF, nevertheless the achievement of sustained sinus rhythm has been shown to improve quality of life and exercise performance.[1] Current antiarrhythmic agents employed in the treatment of AF are limited by their modest efficacy, pro-arrhythmic effects, and long-term toxicity.[2–5] Dronedarone is a new antiarrhythmic agent which has been evaluated in many multicentre trials (Table 1).

Dronedarone

Dronedarone is a newer benzofuran derivative having a structural resemblance to amiodarone with two important molecular changes: it lacks the iodine moiety responsible for thyroid dysfunction and it has a methane sulfonyl group that decreases lipophilicity, resulting in a shorter half-life leading to lower tissue accumulation and less long-term toxicity. It is an orally administered drug cleared by non-renal mechanism and a steady-state serum level is achieved in 5–7 days. The bioavailability is relatively low (15%) because of extensive hepatic first-pass metabolism by cytochrome P450 (CYP) 3A4 and CYP2D6, thus requiring twice daily dosing to achieve steady-state serum levels.[6] Dronedarone is a multichannel blocker with electrophysiological properties similar to those of amiodarone. It decreases slowly activating delayed-rectifier K^+ current I (Kr), and inward rectifier potassium current I (K1), L-type Ca^{2+} current I (Ca [L]) and maximum rate of rise of action potential (dV/dt max) with a concentration and frequency-dependent relationship (I [Na]).[7,8] The drug has very little effect on the QT interval, and proarrhythmia has not been observed. In vitro studies have shown a more efficient inhibition of (I [Na]) in atrial myocytes compared to amiodarone showing atrial selective antiarrhythmic properties.[7,9] Dronedarone is an approximately 100 times more potent inhibitor on muscarinic acetylcholine receptor-operated K^+ current IK (ACh) than amiodarone. This property may be involved, at least in part, in its anti-arrhythmic action against AF, as vagal activation is known to play a role in the pathophysiology of AF. Like amiodarone, dronedarone can partially inhibit the effects of stimulation of the beta 2 and alpha adrenoceptor system that may play a pivotal role in the onset of severe ventricular rhythm disturbances.[10]

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Table 1
Summary of trials on dronedarone.

	Inclusion criteria	Follow-up	Patients	Primary end points	Outcomes
DAFNE[20]	Persistent AF	6 mo	270	Time to AF recurrence	Time to AF recurrence increased on dronedarone 800 mg, with a median of 60 days versus 5.3 days in the placebo group ($P=0.001$)
EURIDIS/ ADONIS[11]	Paroxysmal AF	12 mo	615/629	Time to AF recurrence	At 12 months the recurrence of AF/AFL was 64.1% with dronedarone versus 75.2% with placebo ($P<0.001$). Median time to AF recurrence prolonged from 53 days to 116 days
ERATO[13]	Permanent AF	6 mo	174	Mean ventricular rate on day 14	Reduction of 11.7 bpm in ventricular rate at day 14. This effect was sustained for 6 months
ANDROMEDA[16]	NYHA Class III–IV CHF with LVEF <35%	2 mo	627	All-cause mortality or admission from worsening CHF	Trial was prematurely terminated due to excess mortality secondary to the worsening of HF in dronedarone group (HR=2.13)
ATHENA[12]	Paroxysmal or persistent AF or flutter, +age ≥70 years + one or more risk factors	21 mo	4628	Death from all causes and hospitalisation for the 1st cardiovascular event	Primary outcome was 31.9% in dronedarone group versus 39.4% in placebo group (HR=0.76, 0.84; $P<0.001$)
PALLAS[14]	Permanent AF and additional risk factors	3.5 mo	10,800	1. Composite end point of stroke, myocardial infarction, systemic embolism or death from cardiovascular causes 2. Unplanned hospitalisation for a cardiovascular cause or death	Primary end point in 8.2% versus 3.6/100 pt years; HR=2.29. Secondary end point in 25.3 versus 12.9/100 pt years. HR=1.95 Cardiovascular hospitalisations 22.5 versus 11.4/100 pt years. HR=1.97e

AF: atrial fibrillation, AFL: atrial flutter, CHF: congestive heart failure, HF: heart failure, HR: hazard ratio, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association.

Dronedarone in paroxysmal and persistent atrial fibrillation

The first of the studies to evaluate the effectiveness of dronedarone in rhythm control was the EURIDIS and ADONIS trials which were placebo-controlled and identical in design, conducted in European, and non-European centres (USA, Argentina, Canada, South Africa, and Australia), respectively.[11] Both these pivotal trials aimed at assessing the efficacy of dronedarone in the maintenance of normal sinus rhythm after electrical, pharmacological, or spontaneous conversion of paroxysmal AF or atrial flutter (AFL). It was shown that dronedarone reduced the 1 year symptomatic recurrences (77.5% vs 67.1% in the European trial; 72.8% vs 61.1% in the non-European trial) and prolonged the median time to recurrence (41–96 days in the European trial; 59–158 days in the non-European trial). Further, in both the trials, when the recurrence occurred, the mean ventricular rates were much slower compared to placebo (117 beats/min [bpm] vs 102 bpm and 116 bpm vs 104 bpm, respectively). In the period of 1 year, toxic effects related to lung, thyroid and liver were not significantly increased in the dronedarone group. Though, not an intended end point of the study, post hoc analysis showed a decrease in the combined outcome of hospitalisation and mortality. This observation led to the design of the ATHENA trial to evaluate the effect of treatment on all-cause mortality and morbidity in patients with paroxysmal and persistent AF or AFL.[12] It was a prospective, randomised, placebo-controlled, double-blind, trial evaluating the effects of dronedarone versus placebo (ratio 1:1) in patients with paroxysmal or persistent AF/AFL who had additional risk factors like hypertension, diabetes, age >70 years, previous stroke or transient ischaemic attack (TIA), systemic embolism, and left ventricle (LV) dysfunction. This was the largest trial assessing efficacy of an anti-arrhythmic drug in AF population in reduction of cardiovascular outcomes. In the treatment arm, there was a significant reduction in hospitalisations related to cardiovascular events (36.9% vs 29.3%) particularly due to reduction in hospital admissions for AF. There was, however, no benefit in hospitalisations due to heart failure (HF), ventricular arrhythmias and non-fatal cardiac arrest. Numerically there were fewer deaths in the dronedarone arm compared to placebo (139 vs 116). Overall, there was 30% reduction in cardiovascular deaths and 45% decrease in arrhythmia-related deaths. ATHENA specifically excluded patients who had either haemodynamic instability or severe (New York Heart Association [NYHA] Class IV) HF. An interesting observation in this trial was that there was lesser number of ischaemic strokes with the drug though the frequency of haemorrhagic strokes was similar. This decrease in strokes was particularly impressive in those with ≥2CHADS$_2$ score.

Dronedarone in permanent atrial fibrillation

Achievement of adequately controlled ventricular rates is the principal objective in the management of permanent AF. The possibility that dronedarone could have rate-control properties was suggested by the fact that patients in EURIDIS and