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Dronedarone: A New Generation of Anti-arrhythmic Drug for the Treatment of Atrial Fibrillation

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CHAN ET AL.: Dronedarone: A New Generation of Anti-arrhythmic Drug for the Treatment of Atrial Fibrillation. Amiodarone is currently the most effective anti-arrhythmic drug for the treatment of atrial fibrillation. Its chronic use, however, has been associated with serious extra-cardiac adverse effects. Dronedarone is a new anti-arrhythmic drug that does not possess the different organ toxicities associated with amiodarone. With the addition of a methylsulfonyl group and the removal of iodine moieties, dronedarone has lower tissue accumulation and a shorter half-life than amiodarone. Dronedarone is a potent blocker of multiple ion currents, including the rapidly activating delayed-rectifier potassium current, the slowly activating delayed-rectifier potassium current, the inward rectifier potassium current, the acetylcholine activated potassium current, peak sodium current, and L-type calcium current, and exhibits antiadrenergic and coronary vasodilatory effects. Although less effective than amiodarone as a rhythm-control agent, dronedarone has been shown to reduce ventricular rate and AF recurrence and it is the first anti-arrhythmic drug shown to reduce the combined outcome of cardiovascular mortality and hospitalization in AF patients. Dronedarone, however, is contraindicated in patients with moderate to severe heart failure. The most common side-effects associated with dronedarone are gastrointestinal including nausea, vomiting and diarrhea. This article will review the current evidence of safety and effectiveness of dronedarone in treating patients with atrial fibrillation and the position of this new drug in the currently available anti-arrhythmic armamentarium will be discussed. (J HK Coll Cardiol 2010;18:1-10)

Amiodarone, anti-arrhythmic drug, atrial fibrillation, dronedarone

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**Introduction**

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. The prevalence of AF increases with age, from 0.7% in people aged 55-59 years to 18% in those older than 85 years. The number of patients suffering from AF in Hong Kong is expected to be on an increasing trend as the proportion of elderly continues to grow. Although not immediately life-threatening, AF does result in significant morbidity, namely a three-fold increase in the risk of congestive heart failure, a five-fold increase in the risk of stroke and a two-fold increase in mortality.

The integral components of treatment for AF include anticoagulation for stroke prevention and either one of the strategies, namely rate-control or rhythm-control. With the currently available anti-arrhythmic drugs for rhythm-control, no difference in the incidence of mortality or stroke could be found between the two strategies. On the other hand, the strategy of rhythm-control resulted in a higher incidence of hospitalizations and drug-related adverse events.

There is significant advancement in both non-pharmacological and pharmacological treatment for AF in recent years. Catheter ablation, with evolution over 10 years, has been put as a reasonable alternative to pharmacological therapy to prevent recurrent AF in symptomatic patients with little or no left atrial enlargement. On the other hand, dronedarone, a new generation of anti-arrhythmic drug for the treatment of AF, has been tested in different clinical trials with promising results. The present review focuses on pharmacological and electrophysiological features of dronedarone and the results of major clinical studies with this drug.

**Pharmacodynamics and Electrophysiological Properties of Dronedarone**

Dronedarone is a synthetic benzofuran, amiodarone derivative that is structurally modified to reduce toxicities associated with chronic amiodarone therapy. The addition of methylsulfonyl group makes dronedarone more water-soluble and less likely to accumulate in organ tissue while the removal of 2 iodine atoms prevent the accumulation of the drug in the thyroid gland and other organs, thus avoiding the organ toxicities of Amiodarone (Figure 1).

Dronedarone has a complex electrophysiological profile with multichannel-blocking properties. It delays the action potential repolarization by blocking both the rapid and slow component of the delayed rectifier potassium current. The blockade of both channels decreases the risk of early after-depolarization and thus torsades de pointes. Dronedarone has also been shown to block the slow L-type calcium current and the sodium current. In addition, dronedarone also inhibits the muscarinic acetylcholine receptor-operated

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**Figure 1. Chemical structures of dronedarone and amiodarone.** (Reproduced from Singh BN. Amiodarone as paradigm for developing new drugs for atrial fibrillation. J Cardiovasc Pharmacol 2008;52:300-5 with the permission from Wolters Kluwer Health)
potassium current. This may contribute partly to the anti-arrhythmic effect of dronedarone since vagal activation may be important in the pathophysiology of AF in some patients.\textsuperscript{12,13}

Similar to amiodarone, dronedarone has anti-adrenergic effects by antagonizing $\alpha$ and $\beta$-adrenoceptors\textsuperscript{14} and it possesses coronary vasodilating properties.\textsuperscript{15} These pharmacological properties may lead to favourable clinical cardiovascular outcomes.\textsuperscript{16}

**Pharmacokinetics of Dronedarone**

Dronedarone is well absorbed by oral route (70-90\%). Absorption increases by 2 to 3-fold when it is taken with food. Dronedarone undergoes significant first-pass metabolism with subsequent reduction of bioavailability to 15\%. With drug administration of 400 mg twice daily, steady state plasma concentration was reached in 7 days. The clearance of dronedarone is mainly non-renal with a terminal half-life of 24 hours.\textsuperscript{17}

Dronedarone is a substrate for and a moderate inhibitor of CYP3A4.\textsuperscript{18} As a result, dronedarone should not be given with potent CYP3A4 inhibitors like antifungals, macrolide antibiotics or protease inhibitors which may increase dronedarone exposure by as much as 25-fold. When given together with moderate CYP3A4 inhibitors like verapamil and diltiazam, lower doses of concomitant drugs should be used to avoid severe bradycardia and conduction block.

Likely a result of P-glycoprotein-mediated interaction in the kidney, concomitant administration of dronedarone with digoxin results in a 1.7 to 2.5-fold increase in serum concentration of digoxin.\textsuperscript{17} On the other hand, serum level of simvastatin, a CYP3A4 substrate is increased 2 to 4-fold when given with dronedarone.

Dronedarone is also a CYP2D6 inhibitor. It causes a modest increase in bioavailability of metoprolol in CYP2D6 extensive metabolizers.\textsuperscript{18} Like amiodarone, dronedarone leads to partial inhibition of tubular transport of creatinine. This leads to increase in serum creatinine concentration which is not related to reduced glomerular filtration or renal function.\textsuperscript{19}

**Rate-Control With Dronedarone (ERATO)**

In the ERATO (Efficacy and Safety of Dronedarone for Control of Ventricular Rate) study, 174 elderly patients were randomized to receive 800 mg of dronedarone daily or placebo.\textsuperscript{20} All patients had suboptimal rate control defined by a resting heart rate of $\geq$80 beats per minute despite prior rate-control therapy with $\beta$-blockers, digoxin or calcium channel blockers. Majority of patients had structural heart disease but none had severe heart failure.

In the ERATO study, a satisfactory ventricular rate reduction of 11.7 beats per minute at rest and 24.5 beats per minute during exercise was achieved in patients taking dronedarone. However, no change in exercise tolerance was observed in the dronedarone group. There were no adverse interactions between dronedarone and other rate-control drugs or anticoagulants, apart from a 41\% increase in serum digoxin level. While there were no occurrence of organ toxicity or pro-arrhythmia, the general incidence of side effects including gastrointestinal problems were relatively higher in the dronedarone arm compared to the placebo arm.

**Rhythm-Control With Dronedarone (DAFNE, EURIDIS and ADONIS) (Table 1)**

DAFNE (Dronedarone Atrial Fibrillation Study After Electrical Cardioversion) was a prospective, randomized and dose-finding study. Two hundred and seventy patients with persistent AF were randomized to receive dronedarone 400 mg BD, 600 mg BD, 800 mg BD or placebo.\textsuperscript{21} There was a dose-dependent conversion to sinus rhythm in 5.8\%, 8.2\% and 14.8\% of patients in the 3 dose groups, respectively, compared to 3.1\% in the placebo group. Upon failure of conversion to sinus rhythm within 5-7 days of dronedarone treatment, patients were electrically cardioverted. One hundred ninety-nine patients who were in sinus rhythm were planned to take dronedarone for 6 months.

The primary endpoint in DAFNE was the time to
DRONEDARONE

Table 1. Summary of major clinical trials on dronedarone

<table>
<thead>
<tr>
<th>Trial</th>
<th>Subjects enrolled</th>
<th>Follow-up period</th>
<th>Main outcome</th>
<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAFNE</td>
<td>N=270 Persistent AF</td>
<td>6 months</td>
<td>First AF recurrence was 5.8% with 800 mg, 8.2% with 1200 mg and 14.8% with 1600 mg dronedarone vs 3.1% in placebo (p=0.0261)</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>EURIDIS and ADONIS</td>
<td>N=612 in EURIDIS N= 625 in ADONIS Paroxysmal AF</td>
<td>12 months</td>
<td>First recurrence of AF/AFL was 64.1% with dronedarone vs 75.2% with placebo (p&lt;0.001)</td>
<td>Gastrointestinal (diarrhea)</td>
</tr>
<tr>
<td>ERATO</td>
<td>N=174 Permanent AF</td>
<td>6 months</td>
<td>Reduction of 11.7 beats per minute in ventricular rate at day 14 (p&lt;0.0001) - this effect was sustained for the duration of trial (-8.8 beat/minute at 4 months) (p&lt;0.001)</td>
<td>Infections Mild increase in serum creatinine levels</td>
</tr>
<tr>
<td>ANDROMEDA</td>
<td>N=627 NYHA Class III/IV CHF or PND plus LVEF&lt;35%</td>
<td>13 months (including additional 6 months after premature discontinuation of study)</td>
<td>Premature termination of trial due to excess mortality related to the worsening of heart failure in dronedarone group (hazard ratio of 2.13; 85% CI 1.07 to 4.25; p=0.003)</td>
<td>Worsening heart failure Increase in serum creatinine levels</td>
</tr>
<tr>
<td>ATHENA</td>
<td>N=4628 Paroxysmal/persistent AF/atrial flutter plus at least one additional cardiovascular risk factor</td>
<td>21 months</td>
<td>First hospitalization due to cardiovascular events or death was 31.9% in dronedarone group vs 39.4% in placebo group (hazard ratio of 0.76; 95% CI 0.69 to 0.84; p&lt;0.001)</td>
<td>Gastrointestinal (diarrhea, nausea) Increase in serum creatinine levels Rash, bradycardia</td>
</tr>
</tbody>
</table>

AF=atrial fibrillation; NYHA=New York Heart Association; CHF=congestive heart failure; PND=paroxysmal nocturnal dyspnoea; LVEF=left ventricular ejection fraction.

The first recurrence of AF defined as any documented episode of duration ≥10 minutes, during the 6 months of follow-up. Dronedarone 400 mg BD was found to significantly prolong the time to first AF recurrence compared to placebo (60 days vs 5.3 days, p=0.001). The ventricular rates during AF recurrence also decreased significantly and in a dose-dependent manner. After 6 months, 35% of patients taking dronedarone 400 mg BD and 10% of patients in the placebo group were in sinus rhythm respectively. The higher doses of dronedarone 600 and 800 mg BD were found to lead to higher discontinuation rates with no significant incremental effects on maintenance of sinus rhythm, suggesting a bell-shaped dose-effect curve of dronedarone on rhythm-control. DAFNE has established an optimal dose of 400 mg BD of dronedarone for subsequent clinical studies.

The results of DAFNE drove the implementation of two pivotal trials on dronedarone. They were EURIDIS (European Trial in Atrial Fibrillation or Flutter...
Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm) and ADONIS (American-Australian-African Trial With Dronedarone in Atrial Fibrillation/Flutter Patients For the Maintenance of Sinus Rhythm). They were multi-center, placebo-controlled, double-blinded studies with similar designs performed in different parts of the world. The presence of at least one episode of AF within the last 3 months and the presence of sinus rhythm that persisted at least 1 hour preceding randomization were pre-requisites for recruitment. Both studies had a 1-year follow-up period. A total of 1,237 patients were randomized to receive dronedarone 400 mg BD or placebo in a ratio of 2:1. The time to first recurrence of AF or atrial flutter was the primary endpoint.

Combining EURIDIS and ADONIS, dronedarone 400 mg BD was shown to significantly prolong the median times to first AF recurrence compared to placebo (116 days vs 53 days). AF recurrence rates at 1 year was 64.1% in the dronedarone arm and 75.2% in the placebo arm (HR 0.75, 95% CI 0.65-0.87, p<0.0001). On the other hand, 37.7% and 46% of patients in the dronedarone and placebo arms, respectively suffered from symptomatic recurrences (p<0.001). Both studies demonstrated significantly lower mean ventricular rates in the dronedarone arms during AF recurrence compared to placebo arms. There was no significant difference in the percentage of patients reporting adverse events between the 2 groups (67.4% in dronedarone group vs 62.8% in placebo group). Study discontinuation rates due to adverse events were 9.5% with dronedarone and 6.1% with placebo. Gastrointestinal symptoms, primarily diarrhea, were more commonly encountered in the dronedarone group.

The results indicated that dronedarone was effective increasing the time to first AF recurrence (116 days in the dronedarone group compared with 53 days in the placebo group (HR=0.75, 95% CI, 0.65-0.87, p<0.0001) and in reducing ventricular rate. The proportion of patients who remained free of symptomatic AF or AFL after 1 year was 62.3% (25% risk reduction when compared with placebo, p<0.001) in the dronedarone group. Post-hoc analysis also revealed a 27% reduction in all cause hospitalization and death (22.8% vs 30.9%, p<0.01). Even though there was a 2.4% increase in serum creatinine in the dronedarone group, discontinuation rates due to adverse events were low (9.5% with dronedarone and 6.1% with placebo).

**Dronedarone in Heart Failure (ANDROMEDA)**

Dronedarone has been studied in patients with moderate to severe heart failure. ANDROMEDA (Antiarrhythmic Trial With Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease) was a mortality trial in which dronedarone was compared with placebo in patients with moderate to severe heart failure, regardless of presence of AF history. Patients hospitalized with symptomatic heart failure who had suffered at least one episode of dyspnea on minimal exertion or at rest (NYHA Class III-IV) or paroxysmal nocturnal dyspnea within a month before admission were randomized to receive dronedarone 400 mg BD or placebo. Left ventricular ejection fraction ≤35% was a pre-requisite for inclusion. The trial was stopped prematurely 7 months after the first patient had been randomized due to excess mortality in the dronedarone arm. Twenty-five patients (8.1%) in the dronedarone arm and 12 patients (3.8%) in the placebo arm died (hazard ratio 2.13, 95% CI 1.07-4.25, p=0.027) (Figure 2). The excess mortality in the dronedarone arm was primarily due to worsening of heart failure, with the mortality risk highest in those with the most severely reduced left ventricular systolic function. There are a few possible explanations for this observation. Firstly, the small mortality difference of 13 patients between the two arms might have occurred by chance due to early termination of the study. Secondly, potent inhibition of peak sodium current and resultant impairment of ventricular contractility by dronedarone may cause worsening of heart failure. Lastly, a retrospective analysis identified a higher death rate in patients who were withdrawn from angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers in response to a rise in creatinine level with dronedarone. However, the contribution of this to
the increased mortality in the dronedarone arm is uncertain. Regardless of the exact mechanism, ANDROMEDA study does define a subset of patients not suitable to receive dronedarone.

Clinical Cardiovascular Outcome Study for Dronedarone (ATHENA)

The ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from any Cause in Patients with Atrial Fibrillation/Atrial Flutter) trial was a landmark study which evaluated the impact of adding dronedarone to standard rate controlling agents and anticoagulants in the management of AF. The study was designed to compare the effect of dronedarone 400 mg BD with placebo in a randomization ratio of 1:1, on the prevention of cardiovascular hospitalization or mortality. Patients with paroxysmal or persistent AF or atrial flutter and at least one additional risk factor for cardiovascular events, including age ≥75 years, hypertension, diabetes mellitus, prior stroke or transient ischaemic attack, left atrial enlargement of ≥5 cm or depressed left ventricular ejection fraction of <40% were enrolled. The presence of advanced congestive heart failure was one of the exclusion criteria. The primary endpoint was first cardiovascular hospitalization or mortality from any cause and the secondary endpoints included mortality from any cause, cardiovascular mortality and first cardiovascular hospitalization.

With a mean follow-up duration of 21±5 months, 32% of patients in the dronedarone arm and 39% of patients in the placebo arm reached the primary endpoint (HR 0.76, 95% CI 0.69-0.84, p<0.001) (Figure 3). Dronedarone reduced the first cardiovascular hospitalizations by 26% (p<0.001), and cardiovascular mortality and arrhythmic mortality by 29% (p=0.034) and by 45% (p=0.01) respectively. However, all-cause mortality was not significantly different between the two groups.

The rate of drug discontinuation was not significantly different between the groups (12.7% in the dronedarone group vs 8.1% in the placebo group). However, the frequency of gastrointestinal (26.2% vs 22%) and dermatologic (10.3% vs 7.6%) adverse effects and the frequency of increased creatinine levels (4.7% vs 1.3%) were significantly higher in the dronedarone group.
arm compared to the placebo arm. Regarding the incidence of pulmonary and thyroid adverse effects, no significant difference was observed between the two groups.

A post-hoc analysis revealed that patients who received dronedarone experienced a 34% reduction in the risk of stroke (HR=0.66, 95% CI=0.46-0.96, p=0.03) and a 30% reduction in hospitalization due to acute coronary syndrome (HR=0.70, 95% CI=0.51-0.79, p=0.03).24 Interestingly, patients who remained in AF after treatment also experienced improved outcomes with dronedarone and that the benefits of treatment were not limited to patients who were converted to sinus rhythm.25

**Dronedarone versus Amiodarone (DIONYSOS)**

Dronedarone was compared to amiodarone directly with respect to safety and efficacy for sinus rhythm maintenance in patients with AF in DIONYSOS.
Dronedarone (Dronedarone versus Amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation). The study compared dronedarone 400 mg BD with amiodarone 200 mg daily (with loading of 600 mg daily for 4 weeks) during a mean follow-up of 7 months in 504 patients with documented AF of >72 hours for whom cardioversion and anti-arrhythmic drugs were indicated. The primary endpoint was recurrence of AF or drug discontinuation as a result of drug intolerance or lack of efficacy.

In DIONYSOS, fewer amiodarone-treated patients reached the primary endpoint compared with those treated with dronedarone (55.3% vs 73.9%, p<0.001). Dronedarone was less effective in maintaining sinus rhythm compared to amiodarone after cardioversion (AF recurrence post-cardioversion in the dronedarone and amiodarone arm was 36.5% and 24.3% respectively). More gastrointestinal adverse events, namely diarrhea, vomiting and nausea and fewer cardiac adverse events, namely bradycardia (2% vs 6.3%) and QTc prolongation (10.9% vs 20.5%) were noted in the dronedarone arm.

A study comparing dronedarone with other anti-arrhythmic drugs on major morbidity and mortality outcomes in the treatment of AF, using a mixed treatment comparison was recently reported. Dronedarone was compared to other anti-arrhythmic drugs, namely amiodarone, flecainide, propafenone and sotalol in terms of all-cause mortality, stroke and serious adverse events. For all-cause mortality, 8 randomized controlled trials with 8,252 patients and 349 deaths were included. There was no increase in mortality with use of dronedarone compared to placebo. There was significantly less mortality comparing dronedarone with amiodarone (p=0.032) or sotalol (p=0.009). For stroke, 5 randomized controlled trials with 7,034 patients and 138 strokes were included for analysis. Dronedarone was shown to decrease risk of stroke compared to placebo (p=0.015). No significant reduction of stroke was present with use of amiodarone or sotalol compared to placebo. However, no significant difference can be shown in the risk of stroke among different anti-arrhythmic drugs. For serious adverse events, 18 randomized controlled trials with 8,351 patients and 1,433 serious adverse events were included. Compared to placebo, no significant difference was found for all anti-arrhythmic drugs. And there was also no significant difference in serious adverse events between different anti-arrhythmic drugs.

Position of Dronedarone in the Anti-arrhythmic Armamentarium

The safety and efficacy profile of dronedarone in the treatment of AF has been well studied by different clinical trials, namely ERATO, DAFNE, EURIDIS, ADONIS, ANDROMEDA and ATHENA. It is a new anti-arrhythmic drug with acceptable safety and modest efficacy in rhythm-control for AF. It is also an effective drug for rate-control. Dronedarone is less effective than amiodarone in rhythm-control for AF, as shown by DIONYSOS. However, it has a better safety profile with absence of different types of organ toxicities associated with amiodarone. With safety considered to be a priority in the use of anti-arrhythmic drugs for AF, dronedarone has been proposed to be the first-line agent in maintenance of sinus rhythm in different subsets of patients, except in patients with NYHA Class III or IV heart failure. With the unavailability of dofetilide, an adapted form of anti-arrhythmic treatment algorithm for AF in Hong Kong is suggested in Figure 4. Dronedarone, however, has not been incorporated into contemporary practice guidelines by academic bodies or professional organizations. The evidence for choosing dronedarone over other first-line anti-arrhythmic drugs, at present, is still obscure. However, based on the favourable cardiovascular outcomes in ATHENA, dronedarone is particularly preferred in the patient subset with paroxysmal or persistent AF or atrial flutter and at least one additional risk factor for cardiovascular events.

Conclusions

Dronedarone is a new generation of anti-arrhythmic drug for the treatment of AF. It is the first anti-arrhythmic agent shown to reduce the combined
outcome of cardiovascular hospitalization or mortality in patients with AF. Dronedarone has been shown to maintain sinus rhythm with modest efficacy and control ventricular rate satisfactorily during episodes of AF. When compared with amiodarone, dronedarone is less effective in reducing AF recurrence, but possesses better safety profile. Use of dronedarone, however, should be limited to patients without severe heart failure (NYHA class III or IV) as evidenced by ANDROMEDA.

The tolerability profile of dronedarone is good with gastrointestinal symptoms like nausea, vomiting and diarrhea as the most commonly encountered side effects. There is no clinically significant interaction with warfarin. Some patients may experience prolongation of QTc interval but the occurrence of torsades de pointes is rare. The drug may also cause a reversible increase in serum creatinine level but the effect is not associated with a reduction in renal function.

On the basis of the safety and efficacy portfolio of dronedarone and the favourable cardiovascular outcomes from ATHENA, the new anti-arrhythmic drug has been approved by the United States Food and Drug Administration for use in non-permanent AF or atrial flutter to reduce the risk of cardiovascular hospitalization. In clinical practice, taking safety as the priority, dronedarone may be considered the first-line anti-arrhythmic drug for maintenance of sinus rhythm in AF except in patients with moderate to severe heart failure.

References

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