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Efficacy and tolerability of dronedarone for patients with atrial fibrillation

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Abstract

Background: *Dronedarone is a new antiarrhythmic drug used in the treatment of atrial fibrillation (AF). We investigate its efficacy and tolerability in clinical practice.*

Methods: *We identified 208 patients treated with dronedarone for AF at the Northwestern outpatient practice. Charts were reviewed for clinical efficacy and reasons for discontinuation of the drug.*

Results: *The average age was 65.2 ± 10.8 years, 37% females. Paroxysmal, persistent and permanent AF were noted in 46.2%, 51.9%, and 1.9%, respectively. Average ejection fraction was 56.3 ± 9.1%, 12.8% had a history of congestive heart failure, and 10.3% had valvular heart disease. Dronedarone was discontinued in 25 patients after curative catheter or surgical ablation procedure. Of the remaining 183 patients, dronedarone was discontinued in 48.6% after a mean duration of 6.2 ± 6.3 months because of inefficacy (26.2%), side effects (6%), and other reasons (16.4%). For those remaining on dronedarone (n = 94), after a mean of 11.6 ± 6.6 months, clinical efficacy (resolution of or patient-reported improvement in symptoms) was noted in 45.4% patients. On dronedarone therapy, 57.4% had no AF on follow-up (overall efficacy of 29.5%). To evaluate efficacy, ECG only or long-term monitoring were performed in 62.7% and 37.3%, respectively, and found no AF in 69.2 and 48.4%, respectively. There were 3 deaths and 2 transient ischemic attacks (TIA) off dronedarone vs. 1 death, 1 TIA and 2 strokes on dronedarone.*

Conclusions: *Dronedarone has a significant discontinuation rate due to both inefficacy and side effects in clinical practice. Nevertheless, it has moderate clinical efficacy and tolerability in an outpatient population of patients with AF.* (Cardiol J 2013; 20, 5: 486–490)

Key words: dronedarone, atrial fibrillation, efficacy, tolerability

Introduction

Atrial fibrillation (AF) is a common arrhythmia [1] with significant morbidity and mortality [2]. Although management by rate or rhythm control are equally effective therapies in the management of AF [3–5] maintaining sinus rhythm may be beneficial in patients with symptoms or with other comorbidities [6]. Multiple antiarrhythmic drugs are available for use to prevent recurrent AF but are limited by modest efficacy and potentially serious side effects or toxicity [7, 8]. Amiodarone has relatively high efficacy [9] but also has significant risks of pulmonary, thyroid and hepatic toxicity [10–12].

Dronedarone, a non-iodinated benzofuran derivative of amiodarone [13, 14], was designed to

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have a shorter half-life, lower tissue accumulation and less toxicity when compared to amiodarone. Prior prospective studies have shown low efficacy, with AF recurrence rates of approximately 63–65% over 6–12 months [15–17] and a side effect profile that is more favorable than amiodarone [17–19]. However, studies such as ANDROMEDA [20] and more recently, the PALLAS [21] trials revealed serious adverse effects when used in the setting of severe heart failure and permanent AF with an increase in mortality. There are no studies on the efficacy and side effects of dronedarone in clinical practice, outside the setting of a clinical trial. We report the efficacy and tolerability of dronedarone in patients with AF or atrial flutter (AFL) at a single academic institution.

Methods

Patients

From the Northwestern Electronic Data Warehouse, we identified 252 patients who were reported to have been prescribed dronedarone at the Northwestern outpatient practice. We excluded 35 patients for inaccurate medication listing; one patient had the drug only very briefly during a hospitalization; 2 patients were on dronedarone for ventricular tachycardia; 2 patients were treated with dronedarone empirically post-heart transplant and it was discontinued shortly thereafter; 4 patients were excluded for technical reasons. Thus, we report on the 208 patients who had dronedarone initiated for treatment of AF and/or AFL.

The study was approved by the Northwestern University Institutional Review Board.

Study design

Each chart was reviewed for demographic data and prior medical history, type of AF and prior antiarrhythmic agents and interventions. The type of AF was classified as paroxysmal: self-terminating episodes of AF for up to 7 days; persistent: AF lasting more than 7 days and usually requiring some kind of antiarrhythmic therapy or intervention to restore sinus rhythm; and permanent: persistent AF lasting more than 1 year or failure to restore sinus rhythm despite multiple antiarrhythmic therapies. Specific treatment parameters that were collected include clinical efficacy, and reasons for discontinuation of drug. Recurrence of AF, type of monitoring, all-cause mortality, stroke, and transient ischemic attack (TIA) were assessed during follow-up.

Clinical efficacy included resolution of or patient-reported improvement in symptoms of palpitations, exercise intolerance, or dyspnea. Reasons for discontinuation were: inefficacy, side effects, curative procedures (surgical or catheter ablation), and other. Drug inefficacy was specified as discontinuation of dronedarone due to recurrent AF or symptoms/side effects warranting a change in therapy. The most important reason for discontinuation was documented if a subject had more than one reason for discontinuation. Echocardiogram reports were reviewed for evidence of left atrial enlargement, left ventricular hypertrophy, aortic or mitral valve disease, and left ventricular ejection fraction (LVEF). Valvular disease (aortic insufficiency, aortic regurgitation, mitral stenosis or mitral regurgitation) was considered significant if it was reported to be moderate or severe. Renal disease was considered present if the recorded glomerular filtration rate was less than 60 mL/min.

Information on stroke and TIA were obtained through chart review and information on mortality was obtained from the social security death index.

Data analysis

Categorical variables are expressed as absolute numbers and percentages; quantitative variables are expressed as mean ± standard deviation (SD). Proportions were compared using two-proportion Z-test and continuous variables compared using T-test. A $p < 0.05$ was considered significant.

Results

Dronedarone therapy and discontinuation

The clinical characteristics of the 208 patients treated with dronedarone are shown in Table 1. There were 131 (63%) men and 77 (37%) women with an average age of 65.2 ± 10.8 years. Prior stroke was present in 5 (2.4%) patients, 36 (17.3%) patients had known obstructive coronary artery disease, and 7 (3.4%) had prior myocardial infarction. Paroxysmal AF was present in 96 (46.2%) patients, 108 (51.9%) had persistent AF, and 4 (1.9%) had permanent AF. Dronedarone was started primarily for AFL in only 4 (1.9%) patients. The average LVEF was 56.3 ± 9.1%. Congestive heart failure was present in 25 (12.8%) patients and 20 (10.3%) had valvular heart disease.

In 25 patients, dronedarone was discontinued because the patient had undergone a curative catheter or surgical ablation procedure (i.e. a planned discontinuation); these patients are excluded from further analysis. Out of the remaining 183 patients, dronedarone was discontinued in 89 (48.6%) patients after a mean treatment period of

Table 1. Patient characteristics.

	Total (n = 208)	On dronedarone (n = 94)	Dronedarone discontinued (n = 89)	P
Age [years]	65.2 ± 10.8	66 ± 10.1	66.3 ± 11.8	
Caucasian	80.8%	74.5%	86.5%	0.04
Gender (male)	63.0%	64.9	55.1	0.17
Body mass index [kg/m^2]	29.4 ± 6.0	29.5 ± 6.0	29.0 ± 6.1	
Systolic blood pressure [mm Hg]	121.5 ± 16.4	122 ± 15.1	120.3 ± 17.2	
Diastolic blood pressure [mm Hg]	72.2 ± 11.0	72.7 ± 9.7	70.2 ± 11.8	
Current smoker	2.9%	3.2%	3.4%	
Hypertension	55.3%	59.6%	55.1%	
Diabetes mellitus	13.0%	10.6%	12.4%	
Hyperlipidemia	66.3%	67.0%	62.9%	
Renal disease	26.9%	25.5%	31.5%	
History of stroke	2.4%	2.1%	2.2%	
Prior myocardial infarction	3.4%	3.2%	4.5%	
Coronary artery disease	17.3%	13.8%	20.2%	
Type of atrial fibrillation:				
Paroxysmal	46.2%	53.2%	36.0%	0.02
Persistent	51.9%	46.8%	59.6%	0.08
Permanent	1.9%	0%	4.5%	0.04
CHADS II (median)	1	1	1	
Left ventricular hypertrophy	8.2%	11.5%	6.0%	
Left atrial enlargement	39.2%	43.7%	38.6%	
Left ventricular ejection fraction [%]	56.3 ± 9.1	56.2 ± 8.6	56.3 ± 10.1	
Congestive heart failure	12.8%	10.2%	16.7%	
Valvular disease	10.3%	11.5%	9.6%	
Hypothyroidism	20.3%	16.0%	24.7%	
Chronic obstructive pulmonary disease	6.3%	5.3%	9.0%	
Concomitant cardiovascular therapy:				
Beta-blocker	61.5%	66.0%	58.4%	
Calcium channel blocker	15.9%	13.8%	21.3%	
Digoxin,	5.8%	2.1%	10.1%	0.02
ACE/ARB	36.5%	38.3%	41.6%	
Statin	55.3%	57.4%	49.4%	
Anticoagulation	95.2%	96.8%	93.3%	
Prior antiarrhythmics:	53.4%	55.3%	50.6%	
Amiodarone	30.3%	29.8%	31.5%	
Sotalol	15.4%	16.0%	15.7%	
Flecainide	5.8%	5.3%	6.7%	
Propafenone	12.0%	14.9%	4.5%	0.01
Dofetilide	8.7%	3.2%	13.5%	0.01
Prior intervention:	46.6%	46.8%	47.2%	
Cardioversion	30.3%	28.7%	29.2%	
Catheter ablation	18.8%	23.4%	12.4%	0.05
Maze procedure	5.8%	5.3%	7.9%	

ACE — angiotensin converting enzyme; ARB — angiotensin receptor blocker

6.2 ± 6.3 months (range 5 days to 23.6 months). Discontinuation was due to inefficacy in 48 (26.2%) patients. Side effects resulting in discontinuation were reported in 11 (6%) patients and included gastrointestinal complaints (n = 5), rash (n = 1), fatigue (n = 3), weight gain (n = 1) and dizziness (n = 1). Other reported reasons for discontinuation were observed in 30 (16.4%) patients and included following successful cardioversion to sinus rhythm (n = 1), permanent AF (n = 4), cost (n = 2), self-discontinuation (n = 3), bradycardia (n = 2), heart failure, renal and pulmonary function test abnormalities, pauses and junctional rhythm. Follow-up liver function tests were obtained in 102 patients. Liver enzymes were elevated to > 2 times the upper limit of normal in 6 patients but was the sole reason for discontinuation in 2 patients. There was no severe hepatotoxicity.

Table 1 compares patient characteristics between those who remained on dronedarone and those in whom dronedarone was discontinued. We observed differences in race (74.5% Caucasians vs. 86.5%, p = 0.04), paroxysmal AF (53.2% vs. 36.0%, p = 0.02), permanent AF (0% vs. 4.5%, p = 0.04), digoxin use (2.1% vs. 10.1%, p = 0.02), prior propafenone use (14.9% vs. 4.5%, p = 0.02) prior dofetilide use (3.2% vs. 13.5%, p = 0.01), and prior catheter ablation (23.4% vs. 12.4%, p = 0.05).

Follow-up

Ninety-four (51.4%) patients remained on dronedarone for a period of 11.6 ± 6.6 months. Of this group, 70 (74.5%) were concurrently on rate control medications (beta-blockers, calcium channel blockers, digoxin) and 36 (38.3%) had undergone other non-pharmacological interventions (24.5% had direct current cardioversion, 16.0% catheter ablation, and 3.2% surgery/maze procedure). Clinical efficacy was noted in 83 of these patients for a clinical efficacy rate of 45.4% (83/183). On dronedarone therapy, 57.4% had no AF documented on follow-up, for an overall efficacy of 29.5% (54/183). Of those with clinical efficacy, ECG monitoring alone was performed in 62.7% (n = 52) and identified no AF in 69.2% (n = 36). In contrast, long-term ambulatory monitoring was performed in 37.3% (n = 31) and identified no AF in 48.4% (n = 15).

During the follow-up period, death occurred in 1 patient (subdural hematoma from a fall), stroke in 2 patients, and TIA in 1 patient while on dronedarone therapy. Among those patients no longer on dronedarone, there were 3 deaths (2 due to malignancy and 1 of unknown causes) and 2 TIAs.

Discussion

Our results show that dronedarone is a moderately effective drug in clinical practice for the treatment of AF. However, its use is limited by a fairly high discontinuation rate in approximately half the patients treated with this medication in clinical practice. Overall efficacy rates, approximately 30% to 45%, are similar to other antiarrhythmic drugs used to treat AF [7, 9, 22], but less efficacious than amiodarone [9, 17]. No major toxicity was identified in this series. Thus, dronedarone appears to be an effective drug in the therapeutic armamentarium for AF.

Prior prospective trials of dronedarone therapy have shown efficacy rates of 35% to 36% after a follow-up duration of 6 to 12 months [15–17]. In these studies, drug discontinuation due to side effects was reported in only 4–10% of patients. Touboul et al. [15] in the Dronedarone for prevention of Atrial Fibrillation study (DAFNE) reported a 10.8% rate of discontinuation due to adverse side effects. Other reports have shown discontinuation rates due to side effects up to 13% [21, 23]. In the present study, a 6% discontinuation rate for side effects was noted. However, in the practice-based setting of this study, there was a substantial discontinuation rate for multiple reasons aside from side effects. The reported efficacy rates in this study therefore likely represent a lower bound or underestimate of the efficacy of dronedarone. Yet, the efficacy compares favorably to those previously reported.

The type of monitoring dictated how much AF was found on follow-up. A higher incidence of AF is expected with the use of long-term monitoring [24]. Prior studies [15–17] used predominantly ECG based monitoring, often with regular transtelephonic transmissions of routine and symptomatic ECGs. In the current study, almost 40% of the dronedarone treated patients had long-term monitoring which will identify more AF. Importantly, while absence of AF is a major primary endpoint for AF therapy, symptomatic improvement is also a valid goal to achieve in the highly symptomatic patient. This highlights a potential disparity between clinical use and clinical trial efficacy endpoints.

In theory, dronedarone is supposed to have limited hepatotoxicty compared to amiodarone [25]. Although prior studies have not shown any difference compared to amiodarone [17], they are limited due to the relatively short follow-up. The same findings are true when compared to placebo [16, 23]. However, there have been a few recent

case reports of elevated liver enzymes on dronedarone with both hepatocellular and cholestatic liver injury [26]. In this study, a small number of patients with normal baseline liver function had a 2 to 3-fold increase in liver function tests, but there was no severe hepatotoxicity.

Increased mortality from dronedarone has been observed in patients with advanced or decompensated heart failure (ANDROMEDA study, n = 310 treated with dronedarone) [20] and in patients with permanent AF (PALLAS study, n = 1619 treated with dronedarone) [21] after a short median duration of 2 and 3 months of therapy, respectively. The ANDROMEDA study most likely influenced our sample population while the PALLAS study contributed to the discontinuation of the drug in a small number of patients. Most patients in the current report did not meet the criteria for these studies. Although the sample size is relatively small, there were no major adverse events related to the use of dronedarone in this clinical population. The 4 deaths (1 on dronedarone and 3 off dronedarone) that occurred in this study were not likely related to dronedarone use.

Conclusions

In conclusion, dronedarone is a non-iodinated benzofuran derivative of amiodarone [13, 14] thought to have better tolerability compared to amiodarone [17]. Our experience suggests that dronedarone has a significant discontinuation rate due to inefficacy, side effects, and other reasons in clinical practice. Nevertheless, it has moderate clinical efficacy and tolerability in an outpatient population of patients with non-permanent AF.

Conflict of interest: none declared

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