

Flecainide is well-tolerated and effective in patient with atrial fibrillation at 12 months: a retrospective study

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Abstract

Introduction: Current atrial fibrillation (AF) guidelines recommend flecainide as a first-line rhythm control option in patients without structural heart disease. While there is proven efficacy in clinical trials and guideline support, it is hypothesized that flecainide may be underutilized due to negative outcomes in the CAST trial and that adverse effects are less common than previously perceived.

Methods: This retrospective chart review evaluated patients ≥ 18 years initiated on flecainide for AF from August 2011 to October 2016 by a cardiology provider at the study site. Exclusion criteria included: < 5 days of flecainide therapy, AF due to a reversible cause, and inadequate documentation. The primary outcome was efficacy of flecainide at maintaining symptomatic control at 6 and 12 months. Secondary outcomes included characterization of alterations in rhythm control strategies and documented normal sinus rhythm per electrocardiogram at 6 and 12 months.

Results: Of the 326 patients identified, 144 patients were included. After 6 and 12 months, 102 patients (70.8%) and 89 patients (61.8%) of the 144 were symptomatically controlled. Atenolol use ($p = 0.024$), female sex ($p = 0.006$), hypertension ($p = 0.040$), and dronedarone failure ($p = 0.012$) were associated with flecainide discontinuation at 6 months. At 12 months, only previous propafenone failure ($p = 0.032$) was significant. Of the 144 patients, 16 (11.1%) reported adverse effects with dizziness, hot flashes, bradycardia, and headache (1.4% each) being the most common.

Conclusion: Flecainide is a well-tolerated medication, even at 12 months, with very minor adverse effects. These results support the utility of flecainide in guideline recommended patient populations.

Keywords: antiarrhythmics, atrial fibrillation, flecainide, symptomatic control

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Introduction

Atrial fibrillation (AF) is a well-studied cardiac condition that has increasing prevalence. This is problematic as the condition is associated with a 2-fold increased risk of mortality for women and 1.5-fold increased risk for men.¹ According to American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) guidelines for the treatment of AF, the class Ic antiarrhythmic, flecainide, is a

first-line rhythm control treatment option in patients without significant structural heart disease (aortic stenosis, abnormal left ventricular hypertrophy, coronary artery disease, severe heart failure with reduced ejection fraction, moderate heart failure with preserved ejection fraction, and moderate heart failure with “mid-range” ejection fractions) or severe hemodynamic instability.^{1,2} Even with this recommendation from the guidelines, class Ic antiarrhythmics are not utilized to

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the fullest due to limited tolerability reported by patients (dizziness, visual disturbances, dyspnea, nausea, and headache) in addition to the potential for severe side effects (heart blocks and ventricular arrhythmias).²⁻⁴ However, flecainide has the ability to prolong atrial action potential and prevent recurrence in addition to being easily measurable in plasma concentration, which makes it a sound option for the treatment of AF.⁵

Flecainide's decreased use and reported poor tolerability may have stemmed from the CAST trial which was stopped early due to an increased risk of death due to arrhythmia and shock after recurrent myocardial infarction.⁶ The patient population included those with recent myocardial infarction taking flecainide or encainide to suppress premature ventricular contractions. This differs greatly from those who would be candidates for flecainide therapy based on the most recent AF management guidelines, and thus not be as susceptible to the adverse outcomes.^{1,6} As flecainide can be considered a narrow therapeutic index drug, it is of utmost importance to ensure patients on the medication are appropriate (without structural heart disease) and receive regular monitoring of electrocardiograms (ECGs) along with drug plasma levels to further reduce the risk of adverse events.^{7,8}

The greatest risk for recurrence after conversion to normal sinus rhythm is within the first 3–6 months. This can occur in up to as many as 50% of the patients post conversion.⁵ A randomized trial followed patients for 1 year and found that class Ic antiarrhythmics, in combination with a beta-blocker, can reduce recurrence in over 66% of patients.³ This is considerably higher when compared with other older studies that found flecainide to have an efficacy of preventing recurrence of 31–61%.⁹⁻¹¹

While there is clear benefit and guideline support for the use of flecainide, it is hypothesized that the medication may be underutilized and the adverse effects are not observed at the high rates that have been documented previously. The aim of this study is to further evaluate efficacy, safety, and tolerability of flecainide in patients taking the medication for up to 12 months.

Methods

This was a single-center, retrospective study that evaluated patients initiated on flecainide during

hospitalization at Missouri Baptist Medical Center (MBMC), a 450-bed community hospital in Saint Louis, or patients initiated on flecainide as an out-patient by a BJC Medical Group Cardiology provider with an office residing on MBMC's campus between August 1, 2011 and October 1, 2016.

A list of patients was generated based on the presence of an active order for flecainide. Patients were then screened for inclusion criteria (over 18 years of age and diagnosed with AF) and exclusion criteria (received <5 days of flecainide therapy, AF from a reversible cause, and inadequate documentation to assess symptomatic control). Patients were assessed for symptomatic control based on office visit documentation. Informed consent was waived due to the retrospective nature of the study.

The primary outcome was efficacy of flecainide at maintaining symptomatic control at 6 and 12 months. The secondary outcomes were characterization in alterations of rhythm control strategies (e.g. prescribed an alternate antiarrhythmic, rhythm control discontinued, catheter ablation pursued, etc.), proportion of patients successfully maintained on flecainide therapy that were originally referred to have catheter ablation, and efficacy of flecainide at maintaining normal sinus rhythm at 6 and 12 months based on ECG. For the primary outcome, if a patient was still on flecainide and reported no symptoms the medication was considered efficacious.

Descriptive statistics were used for baseline demographics and all outcomes. Chi-square and Fischer's exact were used to assess characteristics with likelihood for discontinuation of flecainide. Analyses were performed with IBM® SPSS® Statistics for Windows.

Results

Of the 327 patients with an active order from August 1, 2011 to October 1, 2016, 144 were included. A total of 27 patients were excluded because they were being treated for an arrhythmia other than AF, 56 patients were excluded due to inability to verify start date, 70 patients were excluded as their charts could not be accessed in the database, 19 patients were excluded due to poor documentation, and 9 patients were excluded because they were on flecainide therapy

for less than 5 days. The baseline demographics of the patients included are summarized in Table 1. The mean age at initiation was 63 years, mean CHA₂DS₂-VAS_c 1.79, and the mean body mass index was 32 kg/m² with an average weight of 94 kg. At baseline, 96.5% (*n* = 139) of patients had paroxysmal AF, 27.8% (*n* = 40) of patients had a prior cardioversion, 13.9% (*n* = 20) had no rate control, and 38.2% (*n* = 55) of patients were on aspirin therapy alone. Sotalol was the most common previously failed antiarrhythmic at 14.6% (*n* = 21), followed by dronedarone at 13.2% (*n* = 19), amiodarone at 7.6% (*n* = 11), propafenone at 4.9% (*n* = 7), and dofetilide at 0.7% (*n* = 1). Patients were not limited by the number of antiarrhythmics they had previously failed, so there were patients who had failed multiple medications. The mean total daily starting and maintenance dose of flecainide was 220 mg.

As seen in Table 2, of the 144 patients included in the study, 70.8% of them (*n* = 102) at 6 months were symptomatically controlled and at 12 months 61.8% (*n* = 89) were symptomatically controlled. At 6 months, 71 of the 109 (65.1%) patients with available ECGs were maintained in normal sinus rhythm. At 12 months, 65 of the 116 (56%) with available ECGs were maintained in normal sinus rhythm. At 6 months, females, previous dronedarone failure, hypertension, and atenolol use were associated with a lack of symptomatic control. At 12 months, only propafenone was associated with a lack of symptomatic control (available in Table 3). Overall, for patients that tolerated flecainide, 93.7% of patients were symptomatically controlled at 6 months and 93.8% of patients were symptomatically controlled at 12 months.

Flecainide was discontinued most commonly due to continued AF symptoms which occurred in 16% of patients (*n* = 23), followed by adverse drug reactions at 11.1% (*n* = 16), patient request at 5.6% (*n* = 8), post cardiac ablation at 4.7% (*n* = 7), Ic atrial flutter at 2.8% (*n* = 4), developed a contraindication at 1.4% (*n* = 2), and one case that did not have a documented reason at 0.7% (Table 4). Of the two patients that developed contraindications, one of the patients developed coronary artery disease and the other had a gastrointestinal bleed leading to the patient to opt for an ablation in order to avoid life-long anticoagulation. The most common adverse effects reported were dizziness, hot flashes, headaches, and

Table 1. Baseline demographics.

Characteristic, <i>n</i> (%)	<i>n</i> = 144
Age at initiation, mean (SD)	63.17 +/- 9.5
Female	68 (47.2)
Weight (kg) (SD)	94.34 +/- 23.4
BMI (kg/m ²) (SD)	31.96 +/- 15.0
Ejection fraction percent, mean (SD)	59.94 +/- 6.1
Paroxysmal AF	139 (96.5)
Tobacco use	10 (6.9)
Prior cardioversion	40 (27.8)
OSA	16 (11.1)
CHA ₂ DS ₂ -VAS _c , mean	1.79 + 1.3
Hypertension	77 (53.5)
Diabetes mellitus	11 (7.6)
Stroke or TIA	3 (2.1)
Vascular disease or CAD	11 (7.6)
Concomitant rate control	124 (86.1)
Beta-blocker	73 (50.7)
Non-dihydropyridine calcium channel blocker	47 (32.6)
Digoxin	13 (9.0)
No rate control	20 (13.9)
Concomitant antithrombotics	141 (97.9)
Apixaban	24 (16.7)
Dabigatran	17 (11.8)
Rivaroxaban	37 (25.7)
Warfarin	8 (5.6)
Aspirin monotherapy	55 (38.2)
Failed antiarrhythmic medication	49 (34.0)
Amiodarone	11 (7.6)
Sotalol	21 (14.6)
Dronedarone	19 (13.2)
Dofetilide	1 (0.7)
Propafenone	7 (4.9)

+/- as those numbers represent the standard deviation of the mean.
AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; OSA, obstructive sleep apnea; TIA, transient ischemic attack; SD, standard deviation.

Table 2. Primary and secondary outcomes.

Outcome, n (%)	n = 144
Symptomatically controlled at 6 months	102 (70.8)
Symptomatically controlled at 12 months	89 (61.8)
Maintenance of NSR at 6 months	71/109 (65.1)
Maintenance of NSR at 12 months	65/116 (56.0)
NSR, normal sinus rhythm.	

bradycardia at 1.4% each ($n = 2$ for each). The complete list of adverse effects can be found in Table 5.

For management after flecainide failure, 19 patients tried a different antiarrhythmic (nine patients switched to amiodarone, four patients to sotalol, three patients to propafenone, two patients to dronedarone, and one patient to dofetilide), 18 patients on rate control alone, 15 patients opted for an ablation, 3 patients underwent

Table 3. Characteristics associated with lack of symptomatic control.

Characteristic, n (%)	Stopped at 6 months (n = 35)	p-value	Stopped at 12 months (n = 49)	p-value
Age \geq 75	5 (14.3)	0.361	8 (16.3)	0.095
Age \geq 65	15 (42.9)	0.514	16 (32.7)	0.326
Female	24 (68.5)*	0.004	28 (57.1)	0.087
Failed amiodarone	3 (8.6)	0.729	5 (10.2)	0.510
Failed sotalol	3 (8.6)	0.247	5 (10.2)	0.285
Failed dronedarone	9 (25.7)*	0.020	8 (16.3)	0.425
Failed dofetilide	---	1.00	---	1.00
Failed propafenone	4 (11.4)	0.06	5 (10.2)*	0.045
Prior cardioversion	10 (28.6)	0.904	16 (32.7)	0.348
Diltiazem use	10 (28.6)	0.555	16 (32.7)	1.00
Atenolol use	5 (14.3)*	0.039	5 (10.2)	0.274
Nebivololol use	---	0.336	---	0.096
Labetalol use	---	1.00	---	1.00
Metoprolol tartrate use	5 (14.3)	0.954	8 (16.3)	0.670
Metoprolol succinate use	7 (20.0)	0.716	10 (20.4)	0.707
Carvedilol use	2 (5.7)	0.248	2 (4.1)	0.605
Digoxin use	5 (14.3)	0.306	6 (12.2)	0.366
Hypertension	24 (68.5)*	0.040	28 (57.1)	0.526
Diabetes	4 (11.4)	0.463	5 (10.2)	0.510
Stroke or TIA	---	1.00	---	0.551
Vascular disease or CAD	3 (8.6)	0.729	4 (8.2)	1.00
CKD	---	1.00	---	1.00
COPD	---	0.572	---	0.300
OSA	4 (11.4)	1.00	6 (12.2)	0.756
ICD	---	1.00	---	0.548

*Statistical significance

CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disorder; ICD, implantable cardiac defibrillator; OSA, obstructive sleep apnea; TIA, transient ischemic attack.

Table 4. Reason for discontinuation.

Reason for discontinuation	Number discontinued, n (%)
ADR	16 (11.1)
Ic atrial flutter	4 (2.8)
Developed contraindication	2 (1.4)
Patient request	8 (5.6)
Continued symptomatic AF	23 (16.0)
Not documented	1 (0.7)
Post ablation	7 (4.7)

AF, atrial fibrillation; ADR, adverse drug reaction.

cardioversion, and 1 patient on anticoagulation alone.

Discussion

The results of the present study are similar to a study published in 2016 that found metoprolol in combination with flecainide was able to prevent symptoms in 66.7% of patients with persistent

AF after 1 year.³ At 12 months, in the present study, 61.8% of patients were symptomatically controlled. This study did not require that patients be on rate control in addition to flecainide, however a large proportion (83.3%) of patients received concomitant rate control therapy with either a beta-blocker or calcium channel blocker. The success of flecainide in the study could have also been attributed to the fact that the patients included were appropriate candidates for the medication. All patients with a history of coronary artery disease were assessed for severity and there were no patients with a recorded reduced ejection fraction <40%.

As seen in the results, there were factors at 6 months (previous dronedarone failure, hypertension, atenolol use, and female) and 12 months (previous propafenone failure) that were associated with lack of symptomatic control. Based on these findings, it would be reasonable to consider options other than flecainide if a patient has previously failed propafenone. This finding can most likely be attributed to a similar mechanism of action (Vaughan Williams Class IC).¹ Previous data suggests that hypertension has a direct association with the incidence of AF and poor blood pressure control is associated with AF recurrence

Table 5. Adverse drug reactions.

ADR	Number experiencing ADR, n (%)	Reported frequencies, % ⁴
Dizziness	2 (1.4)	19–30
Nausea	1 (0.7)	9
Hot flashes	2 (1.4)	Not reported
Dyspnea	1 (0.7)	10
Worsened fatigue	1 (0.7)	8
Diarrhea	1 (0.7)	0.7–3
Syncope	1 (0.7)	1–10
Weight gain	1 (0.7)	3.5
Left bundle branch block	1 (0.7)	4–12
Flecainide toxicity	1 (0.7)	-
Headaches	2 (1.4)	4–10
Bradycardia	2 (1.4)	<1

ADR, adverse drug reaction.

post catheter ablation.^{12–13} Controlling a patient's blood pressure could potentially impact a patient's ability to achieve symptomatic control. In addition, atenolol has been removed from the guidelines as a reasonable beta blocker to utilize in the treatment of patients with hypertension because it is less effective than placebo in reducing cardiovascular events.^{14–15} It is unknown if these results can be extrapolated to patients with AF. A single case study has identified switching from Tenormin to generic atenolol did result in recurrence of AF.¹⁶ Utilization of brand *versus* generic medication (or changing from brand to generic) was not collected in this study. In addition, females have been identified to encounter more adverse effects compared with males.¹⁷ It is unknown why previous dronedarone failure was associated with lack of symptomatic control with flecainide.

While results found in the study are promising, the study does have a variety of limitations. This study was conducted retrospectively at a single-center and conducted predominately in patients with paroxysmal AF. Only about 3.5% of patients had persistent AF. Data collection relied heavily on what had been entered into the chart by providers and was susceptible to a wide array of variability based on the detail of records kept by prescribers and the subjectivity of patients. There was also the potential for sampling bias as the patients that were started on flecainide were ideal candidates and selected by cardiologists and electrophysiologists, rather than primary care providers. Inadvertently, selection bias could also be present based on the high number of patients excluded based on documentation. The study did not have the ability to track compliance of patients taking flecainide to explore a link between continued symptoms and nonadherence. Lastly, there were missing data points as not all information was available for each patient from the chart review conducted.

Conclusions

Flecainide is a well-tolerated medication, even at 12 months, with very minor adverse effects. These results further support the utility of flecainide in guideline recommended patient populations.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Informed Consent

Informed consent was waived due to the retrospective nature of this research.

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