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SAFETY OF OUT-OF-HOSPITAL INITIATION OF FLECAINIDE IN PATIENTS WITH ATRIAL AND VENTRICULAR ARRHYTHMIAS AND STRUCTURALLY NORMAL HEART

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Aim. This study aimed at investigating the safety of out-of-hospital initiation of flecainide in patients presenting with atrial or ventricular arrhythmias and structurally normal heart.

Methods. Patients were followed 1 week, 1 month and 2 months after drug initiation either in person or through phone interviews and were asked to report symptoms suggestive of sustained arrhythmia, syncope, aborted sudden death and/or emergency room (ER) visits. QRS duration and QTc intervals were measured in a 12-lead ECG at each follow up. Patients were asked to fill out a treatment satisfaction questionnaire for medication (TSQM), four weeks after drug initiation.

Results. The mean patient age was 48.5 ± 15.7 years, 36 patients (52%) were females. The most frequent presenting arrhythmia was premature ventricular contractions in 34 (45.3%) patients followed by paroxysmal atrial fibrillation in 22 (29.3%) patients. There was a significant increase in the mean QRS duration (89.9 ± 6.8 msec vs 91.1±7 msec, P <0.001) and the mean QTc interval (417.4 ±10.6 msec vs 418 ± 10.4 msec, P = 0.025) at 1 week compared to baseline. Only one patient (1.3%) had a clinically significant (more than 25%) increase in the QRS duration requiring drug discontinuation. There was no reported life-threatening ventricular arrhythmia, syncope, ER visits or aborted sudden cardiac death. There was 6.7% incidence of cardiac adverse events including conduction system abnormalities and atrial flutter, 4% of patients experienced non-resolving extracardiac manifestations. The overall drug discontinuation rate was 10.7%. The mean TSQM score for effectiveness domain was 70.4 ± 23.8 while the mean of the side effects domain was 94.3 ± 14.6, that of convenience domain was 65.2 ± 10.5 and that of global satisfaction was 72.8 ± 21.8.

Conclusion. Out-of-hospital initiation of flecainide is safe and thus feasible, there was no reported documented or suspected life-threatening ventricular arrhythmias. Cardiac and extracardiac adverse events requiring drug discontinuation was effectively detected through clinical and ECG outpatient follow up.

Key words: flecainide; antiarrhythmic; IC; structurally normal heart; safety

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Flecainide is a class Ic antiarrhythmic drug that inhibits sodium channels, reducing cardiac cell excitability and conduction velocity [1, 2]. Flecainide also blocks ion flow across the sarcoplasmic reticulum, influencing calcium dynamics and stabilizing cardiac electrical activity [3, 4].

Flecainide has multiple indications supported by recent research, among the most common indications are restoration and maintenance of sinus rhythm in patients with atrial fibrillation and control of symptomatic frequent premature ventricular beats [5-8]. However, despite its benefits, flecainide's ability to delay cardiac conduction and hence enhancing spatial heterogeneities of electrical restitution, particularly in patients with structural heart disease, can lead to proarrhythmic side effects [6]. This was evident in the cardiac arrhythmia suppression trial (CAST) study that showed increased mortality in post myocardial infarction (MI) patients receiving class Ic antiarrhythmic drugs [9]. This study paved the way for contraindicating

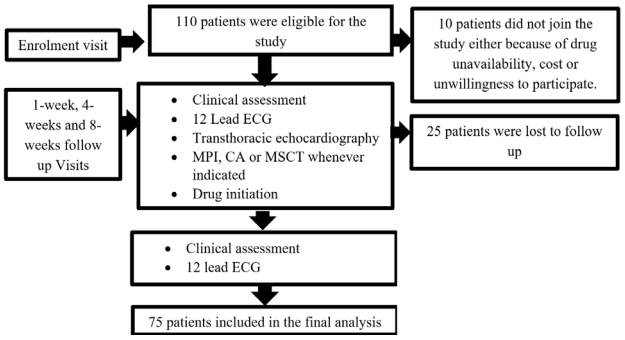

Fig. 1. Study design flow chart.

class Ic antiarrhythmic drugs in post MI patients and for extrapolating this practice to all patients with structural heart disease despite the lack of strong clinical evidence to support this practice. More recently, this dogma has been challenged by studies that support the safety of flecainide in subsets of patients with structural heart disease [10, 11].

The proarrhythmic effect of class Ic AAD tends to cluster shortly after drug initiation [12, 13], thus it is common practice to routinely hospitalize patients for drug initiation under continuous electrocardiographic surveillance. The low incidence of serious pro-arrhythmia in this patient population makes the cost-effectiveness of this practice controversial [14]. Although an expert opinion has suggested that outpatient drug initiation in patients without structural heart disease is safe, no prospective data currently exists to support this opinion [15]. We thought to test the safety of out-of-hospital initiation of flecainide in patients with atrial and ventricular arrhythmias and structurally normal heart.

Table 1.

Baseline characteristics and the presenting arrhythmia in the study population (N=75)

Baseline characteristics	Value
Age, years (Mean±SD)	48.5 ± 15.7
Male, n (%)	36 (48)
Female, n (%)	39 (52)
Diabetes Mellitus, n (%)	5 (6.7)
Hypertension, n (%)	25 (33.3)
Smoking, n (%)	2 (2.7)
Dyslipidemia, n (%)	3 (4)
Presenting Arrhythmia	
Paroxysmal AF, n (%)	22 (29.3)
Atrial flutter, n (%)	3 (4)
Atrial tachycardia, n (%)	4 (5.3)
Premature atrial contractions, n (%)	6 (8)
Premature ventricular contractions, n (%)	34 (45.3)
AVRT, n (%)	2 (2.7)
Combined arrhythmia, n (%)$	4 (5.3)

Note: here and below, AVRT - accessory pathway mediated atrioventricular recurrent tachycardia; $ - paroxysmal AF with PVCs or PACs with PVCs.

METHODS

This study adopted a prospective single-arm experimental protocol, included patients above 18 years old who presented with atrial or ventricular arrhythmia to a specialized arrhythmia clinic affiliated to a tertiary referral hospital. The presenting arrhythmia included atrial fibrillation, atrial tachycardia, premature atrial beats, accessory pathway medicated tachycardia, sustained ventricular tachycardia and premature ventricular beats (PVCs). All patients had to have structurally normal heart and thus were considered candidates for flecainide therapy at the discretion of the treating physician. The heterogeneity of the presenting arrhythmia is thought not to preclude final analysis, since the primary endpoint is a safety endpoint related to the tested drug and the lack of underlying structural heart disease rather than the presenting arrhythmia. The study was conducted during the period from October 2021 to June 2023. The study protocol was approved by the local Research Ethics Board of the hospital to which the clinic conducting the study is affiliated.

Patients were considered to have normal heart based on normal physical examination, normal ECG, normal echocardiography, and no clinical suspicion of coronary artery disease (CAD). If suspected, CAD was ruled out through myocardial perfusion imaging, multi-slice computed tomography coronary angiography, or coronary angiography based on the judgment of the treating physician. Patients were excluded from the study if they have structural heart disease (significant left ventricular hypertrophy, ischemic heart disease, reduced systolic function, and significant valvular heart disease), significant kidney disease (CKD EPI<30 mL/min/1.73 m^2) or significant bradyarrhythmia (sinus node or atrioventricular node diseases).

Study flowchart is displayed in Figure 1, on the day of initiating therapy, all patients were interviewed to obtain baseline demographic data (age and gender), risk factors for CAD such as diabetes mellitus, hypertension, smoking, and dyslipidemia and any reported symptoms that raises suspicion of CAD. General and local cardiac examination were performed. Baseline 12-lead electrocardiography was obtained for calculation of baseline QRS and QTc duration [QT interval was corrected to the heart rate using Bazett's formula [16]] and exclusion of any sinus node or AV node diseases. Baseline echocardiography was performed to exclude structural heart disease.

Table 2.

Post-hoc pairwise comparison between baseline and follow-up values of the QRS width and QT interval in the study population

Items (Mean ± SD)	Baseline	1-week	4-weeks	8-weeks	P-value
QRS width (msec)	89.9±6.8	91.1±7	91.2±7	91.9±8.2	<0.001*
% of increase	0 (0,4.7) 2.3±5.7				
Pairwise comparisons: P1<0.001* P2<0.001* P3<0.001* P4=0.321 P5=0.134 P6=0.118					
QT interval (msec)	417.4±10.6	418±10.4	418.9±9.9	418.9±9.9	<0.001*
% of increase	0 (0,0.7) 0.4±0.6				
Pairwise comparisons: P1=0.02* P2<0.001* P3<0.001* P4<0.0018* P5<0.001* P6=1.000					

Note: * - significant P value. P1(baseline vs 1-week), P2 (baseline vs 4-weeks), P3 (baseline vs 8-weeks), P4 (1 week vs 4-weeks), P5 (1-week vs 8-weeks), P6 (4-weeks vs 8-weeks).

Flecainide was administered out of hospital at a dose of 50 mg twice daily and was uptitrated, if needed, to 100 mg twice daily at the 1-week visit based on improvement of symptoms and the first follow up ECG. Patients were followed up at 1-week, 4-weeks and 8-weeks, either in person or through telephonic interviews. Each follow up visit, patients were evaluated for symptoms suggestive of aggravation of the presenting arrhythmia or development of new arrhythmia including syncope, aborted sudden cardiac death and/or emergency room (ER) visits. Twelve-lead electrocardiography was reviewed, at each follow up, with emphasis on calculation of the QRS duration and QTc duration. Holter was requested if clinically indicated.

Treatment Satisfaction Questionnaire for Medication (TSQM version 1.4-IQVIA) was sent for patients to fill out at the 4-weeks follow up to evaluate patients' satisfaction. A license agreement was obtained from the company that owns the copyright. The TSQM has 14 questions and encompasses four domains: Effectiveness, Convenience, Side Effects, and Global Satisfaction. We adhered to the standard guidelines for implementing TSQM, including administering it in the respondents' native language thus the Arabic version was utilized [17], allocating enough time for the completion of the TSQM and ensuring that the font size of the TSQM text was sufficient for easy readability. The responder was required to indicate their degree of satisfaction or dissatisfaction with the drug for each item. This was done by inserting a single tick mark next to the answer that best matched their personal experiences, based on the previous 4 weeks. We categorized the responses to the Questions of each domain as "highly satisfied," "satisfied," "neutral," "dissatisfied," or "highly dissatisfied" based on the Likert scale.

The four previously mentioned domains of the TSQM were calculated. The scores for each domain are calculated by summing the TSQM items within each domain and then converting the combined score into a numerical value between 0 and 100, the higher being the better. The TSQM itself doesn't typically have a universal or standardized cutoff point to determine a threshold for treatment satisfaction.

The primary endpoint of this study was symptoms suggestive of life threatening proarrhythmia and clinically relevant ECG changes necessitating drug termination. Secondary objectives included investigating minor adverse events that does not necessitate drug termination, patient satisfaction according to the TSQM and flecainide efficacy in controlling atrial and ventricular arrhythmias.

Statistical analysis

The study sample size at an effect size of 0.25 based on the difference from constant (binomial test, one sample case) with two-tailed calculation and a constant proportion of 50%, at alpha error of 0.05, and a power of 95%. We found that the sample size was 65 patients then we calculated a 20% dropout. The analysis was conducted using Statistical Package for Social Science (SPSS v. 27) on Windows. Quantitative variables that follow a normal distribution are often stated using the mean and standard deviation (SD), whereas non-parametric distributions are expressed using the median and interquartile range. The qualitative variables were represented using numerical values in the form of numbers (No.) and percentages (%). Chi-squared test (or Fisher's exact) was used to detect the difference in both groups regarding the categorical variables. Comparison between 2 subgroups regarding normally distributed scale variables was done by T-test and that of not normally distributed was done using the Mann-Whitney U test. Comparison between 3 subgroups regarding normally distributed scale variables was done by One-Way ANOVA and that of not normally distributed was done using the Kruskal Wallis test. The significance of the results was assessed in the form of a P-value when it was < 0.05.

RESULTS

Baseline characteristics of the study population

One hundred fifteen patients assessed for eligibility to our study, 5 patients were excluded because of not meet-

Table 3.

Clinical predictors of flecainide adverse events

Risk factors	No adverse events (n=59)	Adverse events (n=16)	P-value
Age (Median [IQR])	48 (37,57)	53 (40,65)	0.295 (MW)
Male, n (%)	29 (49.2)	7 (43.8)	0.908 (MW)
Diabetes Mellitus, n (%)	5 (8.3)	0 (0.0)	0.128
Hypertension, n (%)	21 (35.0)	4 (26.7)	0.540
Smoking, n (%)	2 (3.3)	0 (0.0)	0.341 (FET)
Dyslipidemia, n (%)	1 (1.7)	2 (13.3)	0.100 (FET)
Paroxysmal AF, n (%)	19 (32.2)	3 (18.8)	0.178
Paroxysmal atrial flutter, n (%)	3 (5.0)	0 (0.0)	
Atrial tachycardia, n (%)	3 (5.0)	1 (6.3)	
PACs, n (%)	5 (8.4)	1 (6.3)	
PVCs, n (%)	25 (42.4)	9 (56.3)	
AVRT, n (%)	2 (3.4)	0 (0.0)	
PFCs and PVCs, n (%)	1 (1.7)	0 (0.0)	
Paroxysmal AF and PVCs, n (%)	1 (1.7)	2 (12.5)	
Flecainide dose 50 mg BD, n (%)	18 (30.5)	3 (18.8)	0.440
Flecainide dose 100 mg BD, n (%)	41 (69.5)	13 (81.3)	
Baseline QRS width (Median [IQR])	90 (85,95)	85 (85,90)	0.295
Baseline QT width (Median [IQR])	410 (410,428)	415 (410,430)	0.829

Note: AF - atrial fibrillation; PACs - premature atrial contractions; PVCs - premature ventricular contractions; IQR - interquartile range; FET - Fisher exact test; MW - Mann Whitney U test

ing the inclusion criteria, 10 patients couldn't initiate flecainide either because of availability or cost limitations, 25 patients were lost to follow-up, and thus 75 patients were included in the final analysis. Mean age was 48.5±15.7 years, 36 patients (48%) were males. Five (6.7%) patients were diabetic and 25 (33.3%) were hypertensives. The most common presenting arrhythmia was PVCs in 34 (45.3%) patients followed by paroxysmal atrial fibrillation (PAF) in 22 (29.3%) patients. Following the first follow up visit, 54 (72%) patients were maintained on 100 mgs flecainide twice daily dosing, while 21 (28%) patients were maintained on 50 mgs twice daily dosing. Baseline characteristics of the study population is shown in Table 1.

Electrocardiographic data

The mean baseline QRS width was 89.9±6.8 msec while the mean baseline QTc interval was 417.4±10.6 msec. There was a significant increase in the mean QRS duration (89.9 ± 6.8 msec vs 91.1±7 msec, P <0.001) and the mean QTc interval (417.4 ±10.6 msec vs 418 ± 10.4 msec, P = 0.025) at the 1-week follow up compared to baseline, however, there was no further increment in the QRS duration beyond the first follow up visit Table 2.

At the end of follow up, 54 (72%) had no change of QRS duration, 4 (5.3%) had to < 5% QRS prolongation, 15 (20%) patients had 5-10 % QRS prolongation, only one (1.3%) patient had 10-25% QRS prolongation and only one (1.3%) patient had > 25% QRS prolongation requiring discontinuation of the drug (44.5% increment from baseline). Fifty-three (70.7%) of patients that had no change in QTc interval from baseline and 22 (29.3%) of patients less than 5% QT prolongation from baseline.

Proarrhythmia, side effects, efficacy and patients' satisfaction

There were no reported symptoms suggestive of aggravation of the presenting arrhythmia or development of life-threatening arrhythmia including syncope, aborted sudden cardiac death and/or ER visits. Two patients (2.7%) developed complete right bundle branch block, 1 patient (1.3%) developed asymptomatic tri-fascicular block, 1 patient (1.3%) developed marked PR prolongation, and 1 (1.3%) patient developed asymptomatic transient (30 seconds) atrial flutter with 1:1 atrioventricular conduction documented in a Holter monitor. The most common extracardiac side effects were blurred vision in 3 (4%) patients, insomnia in 2 (2.7%) patients and gastrointestinal symptoms in 2 (2.7%) patients, dizziness in 2 (2.7%) patients, other less common non-cardiac adverse effects occurred in 2 (2.7%) patients including weight gain and eyelid tremors. The drug was discontinued in eight (10.7%) patients due to adverse effects, in 5 (6.6%) patients due to cardiac adverse effects (conduction system abnormalities and atrial flutter) and in 3 (4%) patients due to blurring of vision and insomnia. The occurrence of adverse events was independent of the patients' baseline characteristics, the presenting arrhythmia, baseline QRS and QTc duration and flecainide dose Table 3.

Table 4 shows the efficacy of flecainide evidenced by reduction of the arrhythmia burden reduction in patients who underwent follow up Holter monitor at the discretion of the treating physician. The mean effectiveness domain of the TSQM score was 70.4 ± 23.8 while the mean side effects' domain was 94.3±14.6, that of the convenience domain was 65.2±10.5, and that of global satisfaction was 72.8±21.8. There was no statistically significant difference between in all domains of the TSQM comparing atrial to ventricular arrhythmias Table 5.

Table 4.

Efficacy of flecainide evidenced by arrhythmia burden in patients undergoing Holter monitor before and 8-weeks after therapy

Presenting arrhythmia	Number of patients	Baseline	At follow up	P-value
PVCs	22	13.5% (8.2-20.5)	5% (1-5)	0.001
PACs	3	10% (3.310)	10% (1-10)	0.656
Paroxysmal AF	9	9/9 (100%)	2/9(22.2%)	0.001
Atrial flutter	2	2/2 (100%)	0/2 (0%)	0.083
Atrial tachycardia	2	2/2 (100%)	0/2 (0%)	0.083

Note: data represented by percentage (%) median (Interquartile range) for PVCs and PACs and by for number of episodes for paroxysmal AF, atrial tachycardia and flutter episodes.

Table 5.

TSQM score based on the type of presenting arrhythmia

TSQM Domain	Presenting Arrythmia#		P-value
	Atrial (n=35)	Ventricular (n=34)	
Effectiveness (Mean ± SD)	64.6±22.1	67.1±24.3	0.704
Side effects (Mean ± SD)	95.7±11.9	94.2±14.5	0.215
Convenience (Mean ± SD)	74.3±10	73.9±11.3	0.993
Global satisfaction (Mean ± SD)	62.3±21.1	63.2±23.2	0.902

Note: # - excluding patients with accessory pathway medicated tachycardia and patients with combined arrhythmia.

DISCUSSION

Flecainide is a class Ic antiarrhythmic drug that blocks sodium channels. The drug is effective for the treatment of both atrial and ventricular arrhythmias [5-8]. There has been reports about increased mortality in post MI patients [9], this raised concerns about its safety in patients with structural heart disease and led to the common practice of initiating it in-hospital in many centers worldwide even in patients with structurally normal heart [13, 18-20]. This prospective single-arm cohort study explored the safety of outpatient initiation of flecainide in patients with apparently structurally normal hearts in patients presenting with atrial or ventricular arrhythmia.

The present study found a statistically significant increase in the QRS duration and QTc interval at the 1-week follow up visit of drug initiation compared to baseline. There were no reported symptoms suggesting life-threatening

ventricular arrhythmia, including syncope, aborted SCD and/or ER visits. There was 6.7% incidence of cardiac adverse events including conduction system disease and atrial flutter, 4% of patients experienced non-resolving extracardiac manifestations. The overall drug discontinuation rate was 10.7%.

To our knowledge, the current study is the first that investigates the safety of out-of-hospital initiation of flecainide as long-term therapy in patients with structurally normal hearts. There was no life-threatening pro-arrhythmia, cardiac and extracardiac side effects requiring drug discontinuation were detected through scheduled follow up visits thus proving the safety and feasibility of this approach. One study, investigated the use of flecainide as an out-of-hospital, pill in the pocket therapy in 165 patients and reported that 12 (7%) patients had drug adverse effects, one 1(0.6%) patient and atrial flutter with rapid ventricular response and the rest of the adverse effects were non cardiac including nausea, asthenia and vertigo, thus advocating for the drug safety in the out-of-hospital setting. However, this study investigated a pill-in-the-pocket single dose approach rather than initiation of long-term therapy [21].

Previous studies reported a multitude of side effects associated with flecainide, with comparable incidences to those in our study. In patients without structural heart disease, flecainide is relatively well-tolerated, with dizziness (15-20%) and visual abnormalities such as blurred vision and difficulty focusing (up to 15%) being the common adverse effects [22] A comparative study by Tamargo et al. noted adverse effects like angina symptoms (1%), hypotension (0.8%), diarrhea (0.7%), headache (2.0%), and nausea (1.6%) [19]. Central nervous system side effects such as dizziness, visual disturbances, headache, and nausea are frequent, though severe central nervous system toxicity is rare [23]. In a study by Oudijk et al., negative inotropic effects occurred in 2 to 5% of patients [24]. In this study, none of the baseline clinical and electrocardiographic characteristics, flecainide dose or the presenting arrhythmia correlated with the occurrence of adverse events. In one study conducted in the pediatric population, younger age and lighter weight were associated with higher plasma concentrations of flecainide, potentially increasing the risk of adverse effects, this was likely because of significantly less mean age and body weight in this pediatric patient group [25].

Study limitations

The present study is limited by being a single-arm non-randomized cohort study thus future randomized controlled studied is needed to further investigate this research question. The relatively short time of follow up is another limitation which may result in underreporting of some of the drug adverse events particularly the extracardiac manifestations. A third limitation is the relatively high drop-out rate in follow up (25 out of 100 patients), this is more likely to be explained by logistic factors that hinders communication due to continuous relocation and change of medical facilities characteristic to this young active population rather than being related to life threatening events, particularly that the rest of the cohort showed no life threatening events.

CONCLUSION

In conclusion, this study demonstrates the safety and feasibility of out-of-hospital initiation of flecainide in patients with structurally normal hearts presenting with atrial or ventricular arrhythmias. Consistent with existing literature, flecainide prolonged the QRS complex and the QT interval at drug initiation, however, there was no report of any symptoms suggesting life-threatening ventricular arrhythmia. Drug adverse effects that warranted discontinuation were around 10.7% and were effectively detected through clinical and ECG outpatient follow up.

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