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Original Research Article

A Randomized Clinical Trial on Efficacy and Safety of Flecainide Alone and in Combination with Metoprolol in the Treatment of Atrial Fibrillation

M. Hitesh Reddy[1], Niketan. D[2], P. Saifulla[3]

[1]Assistant Professor, Department of General Medicine, Viswabharathi Medical College, Kurnool

[2]Associate Professor, Department of General Medicine, Viswabharathi Medical College, Kurnool

[3]Assistant Professor, Department of General Medicine, Viswabharathi Medical College, Kurnool

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Corresponding author: Dr Shamsheer Khan
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Abstract

Introduction: To study the role of Flecainide alone, flecainide and Metoprolol and Metoprolol alone in attaining sinus rhythm, prevention of recurrence of Atrial Fibrillation (AF) in acute, persistent and paroxysmal AF patients.

Objectives: To measure the resting and peak heart rates, exercise duration, maximum workload, sinus rate at the onset of arrhythmias, recurrence rate and exercise induced arrhythmias.

Materials: 68 patients with AF studied over a period of 2 years with three anti-arrhythmic drug therapies **(**Metoprolol-22, Flecainide-23 and Combination therapy-23). Demographic details and clinical parameters were taken as variables: Resting and peak heart rates, exercise duration, maximum work load, sinus rate at the onset of arrhythmias, ECG changes (PR interval, QT interval and QRS complex), LV impairment and exercise induced arrhythmias.

Results: 68 patients with AF were divided in to 3 groups (Metoprolol-22, Flecainide-23 and Combination therapy-23) of ant-arrhythmic therapies by randomization where the three groups were matching in relation to age, gender, duration of AF prior to the study, recruitment period after initiating the anti-arrhythmic drugs, duration of follow up, side effects, deaths and the clinical categories of AF**.** The clinical parameters of the three groups analyzed with Pearson R calculator and found to be significant (p value was 0.0001; p significant at <0.05). Exercise induced AF was observed in all three groups.

Conclusions: Flecainide was found to be a safe, effective anti-arrhythmic drug which could be used as a monotherapy or in combination with Metoprolol with low side effects and no mortality. Combination therapy with Metoprolol gave an added advantage of controlling the heart rate both at rest and at exercise and preventing exercise induced arrhythmias.

Keywords: Atrial Fibrillation, Heart Rate, Sinus Rhythm and Tachycardia

Background

Atrial Fibrillation (AF) has a worldwide prevalence of 0.5 to 5.5% [1,2]. In India different studies showed a variation of 0.1 to 1.6% prevalence of AF [3, 4]. The most probable cause of AF was Ischemic heart disease in Britain [5] and in India it was Rheumatic heart disease. (3] If AF occurs with Myocardial Infarction, it occurs within one day but self-limiting [6]. Patients are to be observed for rapid development of AF and hemodynamic compromise [6]. AF also is common marker of scarred and compromised myocardium with ventricular dysfunction further leading to Heart failure [6]. AF could result in tachycardia followed by angina and cardiac Ischemia and finally heart failure. AF predisposes to Acute Myocardial Infarction (AMI) in ten to fifteen percent; an indicator of widespread myocardial damage and leading to poor prognosis and mortality [7]. More than half of the patients with AF showed high blood pressure (>150/100 mm Hg) for more than 10 years and together contributed for strokes and thromboembolism, especially when left ventricular hypertrophy was present. (8] ECG was a guide for screening left ventricular hypertrophy diagnosed by changes in S wave in V1, R wave in V5 or V6 equal or more than 35 mm). LVH was diagnosed on 2D-Echo by measuring the left ventricular mass index [8]. Transcatheter ablation is being used frequently for the treatment of AF which is refractory to anti-arrhythmic cardiac drugs, but anti-arrhythmic drugs have a major role either alone or in combination with transcatheter ablation [9]. Flecainide was approved in 1984 as an Anti-arrhythmic and approved by FDA mainly to combat the persistent VT (Ventricular Tachycardia) and later also used in AF, acute cardio version and for achieving sinus rhythm [10]. The CAST study in 1991 had published disadvantages of Flecainide due to unforeseen mortality among their subjects; but later on found that the deaths were due to low left ventricular ejection fraction and impulse disturbances in intraventricular (IV) areas of subjects [11]. But other studies later and in recent times have shown good clinical efficacy of this drug and highlighted the best use in cardiology by stating the indications and contraindications and required monitoring [12]. The drug Flecainide is absorbed from GIT up to 85 to 90% within 1 to 3 hours [13] and the peak serum concentration reached was more than 0.2 to 1mcg/mL with nearly half of it bound to plasma protein. It is metabolized in the liver by cytochromes CYP1A2 and CYP2D6.

It is excreted through kidney entirely. The half-life is about 20 h (range: 12–27 h). The mode of action of Flecainide was principally obstructing the open-state fast inward Na^+ channel known as Nav 1.5. This block occurs in a rate- and voltage-dependent manner. Rise of phase 0 of the action potential was also blocked in His-Purkinje tissue and ventricular muscle [14]. In this manner Flecainide extends the duration of action potential and effective refractory period in ventricular fibers. Prolonged QT interval syndrome type 3 also can be treated with Flecainide in addition to cardiomyopathy of arrhythmic origin and prolonged QTc [15]. The necessity to use anti-arrhythmic cardiac drugs in AF was to control the ventricular rate, to treat the symptoms and hemodynamic instability and cardiomyopathy [16].

The common symptoms are breathlessness, weakness, palpitations, discomfort in the chest and dizziness; these symptoms are directly or indirectly related to tachycardia and irregular ventricular rate. Associated hemodynamic changes consist of fall in blood pressure, cardiac output and elevation in left atrial pressure [17]. In AF the rate of heart and rhythm of heart have to be regularized.

The drugs prolonging the conduction through AV node reduce the heart rate and the rhythm is achieved by cardio-version, anti-arrhythmic drugs and non-pharmacological methods like catheter ablation [17]. Metoprolol being cardio-selective beta-1-adrenergic receptor without any effect on beta-2 receptors reduces the heart rate with oral doses less than 100mgs. The negative inotropic and chronotropic actions of Metoprolol reduce the cardiac output without intrinsic sympathomimetic activity and membrane stabilizing activity. Metoprolol is completely absorbed from the GIT on oral consumption [18]. 50% of the drug crosses the liver during first pass. Half-life of Metoprolol is 3 to 4 hours on oral intake for non-extended release tablets. Metoprolol is excreted mainly through kidneys [18]. Metoprolol can be administered either oral or intravenous routes. The present study was conducted to observe the efficacy of Flecainide and metoprolol as a combination to prevent the recurrence of Atrial Fibrillation in persistent AF patients.

Materials

A prospective, randomized open blinded study was conducted over a period of 2 years from Aug 2018 to July 2020 in a tertiary care Hospital of Andhra Pradesh. 68 patients with symptomatic Atrial Fibrillation attending the Department of General Medicine were included as per the inclusion criteria mentioned below.

Inclusion criteria: Patients aged above 18 years included. Patients of both the genders were included. Patients diagnosed with Atrial Fibrillation (AF) within 1 year were included. Patients with ECG showing at least once within 12 months an episode of AF lasting for more than 30 seconds were included. Patients with previous history of transient ischemic attack, strokes were included. Patients with arterial hypertension with resting blood pressure more than 150/90 mmHg were included. Patients with Diabetes Mellitus and impaired glucose tolerance test were included. Patients with severe coronary artery diseases, CABG, previous MI and PCI were included. Patients with CKD were included. Patients willing to join the study with signed informed consent only were included. Patients with stable Heart Failure with ejection fraction less than 50% were included. Patients with Left ventricular hypertrophy with more than 15mm thickness were included.

Exclusion Criteria: Patients with low life expectancy (<1 year) were excluded. Patients with underwent clinical trials within 2 months of this study were excluded. Patients with pregnancy, lactation were excluded. Patients with history of immune deficiency or drug abuse were excluded. Patients with previous AF ablation or surgery for AF were excluded. Patients who were on amiodarone and requiring escalation therapy were excluded. Patients with poorly managed congestive heart failure were excluded. Patients who have undergone cardiac surgery 2 months before were excluded. Patients who were on verapamil or class I or class III anti-arrhythmic drugs were excluded. Patients with untreated thyroid dysfunction were excluded. An institutional ethic committee clearance was obtained and ethics committee approved signed consent form was used.

Practical inclusion: Patients with untreated AF with heart rates above 150 /minute was decided whether to control the rate or rhythm. Patients with sinus rhythm for 6 months after first cardio version were initiated in to the study. Patients with relapse of AF after cardio version were included. 68 patients were randomized using random numbers obtained from randomization.com form the internet. An open blinded method was used in all the three groups: In Group A 22 patients were given IV and /or oral Metoprolol, In Group B 23 patients were given Flecainide by IV and oral routes. In Group C 23 patients

were given a combination of IV and oral Metoprolol and Flecainide.

Drug Dosage: In group A: (Metoprolol group): Metoprolol dosage was for **acute ventricular rate control:** IV: 2.5 to 5 mg over 2 minutes; repeated the dose every 5 minutes as needed (maximum total dose: 15 mg.) Care was taken to initiate cautiously in patients with concomitant heart failure. In patients requiring maintenance of ventricular rate control the immediate release Metoprolol was used on Oral administration of 25 to 100 mg twice daily. Extended release metoprolol succinate on *o*ral was given in 50 to 400 mg once daily dose.

In Group B: (Flecainide group): IV Flecainide 2mg/Kg over a period of 30 minutes for acute AF was administered. For other types of AF, Tab Flecainide 50 mg 12th hourly and the dose increased by 50 mg every fourth day to achieve sinus rhythm. (For patients >70 kg the dose was 300mg, for 40 to 70 Kg patients it was and for patients 40 to 70 kg it was 5 mg/kg).

Group C: (combined Flecainide and Metoprolol group): patients received both Metoprolol and Flecainide as a combination (similar to the doses used in group A and B).

The clinical parameters observed were (Variables): Resting and peak heart rates, exercise duration, maximum work load, and sinus rate at the onset of arrhythmias, ECG changes (PR interval, QT interval and QRS complex), LV impairment and exercise induced arrhythmias. The total duration of intake of anti-arrhythmic drugs (recruitment period) was varying from 21 to 22 months. All the patients were also given concomitant medicines such as oral anticoagulation drugs: Warfarin sodium (ratio of 2.1 to 3.0) from three to six weeks after cardio version or diagnosis of AF.

Statistical Analysis: All the data was analyzed using standard statistical methods and level of significance was tested using student‘t’ test. Mean standard deviation and percentages were used to express the values of the variables. Statistical significance was calculated using one way repeated measure ANOVA calculator with p value less than 0.05 taken as significant. Statistical analyses were done using Microsoft excel software.

Results

68 patients with AF were distributed in to 3 groups were allotted by random numbers allotted by randomization.com software form the internet. The demographic details and clinical parameters observed during the study period were tabulated in the Table 1. All the three groups were matching other, without gross variation in the age, gender, duration of AF prior to the study, recruitment period after initiating the anti-arrhythmic drugs, duration of follow up, side effects, deaths and the clinical categories of AF (Table 1). There were 23 patients with acute AF, 20 patients with paroxysmal AF and 25 patients were on follow up after AF. There was no statistical significant difference among the three groups patients (p value >0.05; p significant at <0.05). The mean duration past the diagnosis of patients with AF was 11.8±2.35 months with a variation of 11.6 to 12 months. The mean values of the clinical parameters observed in the three groups of treatment schedules were analyzed for statistical correlation using Pearson R calculator to calculate the p value, the R value was 0.9998 and the p value was 0.0001 (p taken as significant at <0.05). There was correlation between group A and B and also between Group B and C in this study. (The p value was 0.00001 in both the correlations). There were no recurrences or deaths in any of the three groups. There were exercise induced AF in all the three groups (02 in group A ,01 in Group B and 04 in Group C), (Table1). Remaining 19 (82.60%), 21 (91.30%) and 22 (95.65%) patients of Groups A, B and C respectively, obtained sinus rhythm during

their follow up examinations over the period of two years of the study.

Table 1: Showing the incidence of age, gender, dosage, side effects, clinical parameters and deaths among the study groups (n-68; Agroup-22, B group-23 and Group C-23). Significant correlation between the three studies; p value 0.0001

Variable	Group A Number (%)	Group B Number (%)	Group C Number (%)	Total	P value
Mean Duration of AF in months	11.6	11.9	12	--	--
Drug used	Metoprolol	Flecainide	Flecainide & Metoprolol	--	--
Number	22 (32.35)	23 (33.82)	23 (33.82)	68	0.112
Recruitment period (months)	22	21	21	64	0.239
Age 18- 28 28-48 48-58 58-68 68-78	 03 07 06 03 03	 04 05 04 05 03	 05 04 06 04 02	 12 16 16 12 08	0.287
Gender Male Female	 13 09	 12 11	 14 09	 39 29	0.114
Sub types of AF- Number **Acute AF (drugs used)**	**08** <15 mg. IV+ 200 to 300mg.oral	**08** <2mg/Kg.. IV+ 50 to 100mg.oral	**07** <15 mg. IV. Flecainide over 30 minutes + IV 2.5 to 5 mg Metoprolol over 2 Mins.	23	0.0001
Number **Paroxysmal AF (drugs used)**	**07** 200 to 300mg.oral	**05** 50 to 150 mg oral	**08** Flecainide 50 to 150 mg oral +200 to 300mg. Metoprolol oral	20	
Number **Follow up period (drugs used)**	**07** 200 to 300mg.oral	**10** 50 to 150 mg. oral	**08** Flecainide 50 to 150 mg oral +200 to 300mg. Metoprolol oral	25	
Follow up	21	21	21	63	0.213
Side effects	01	03	02	06	
Clinical parameters **Mean values, SD** resting heart rate peak heart rates	 75±3.24 126±5	 81±2.83 130±6	 71±5.35 121±5	 -- --	0.0001

Exercise duration (Mins.) maximum work load (MET) sinus rate at the onset of AF Conversion to Atrial flutter	315±9 13±2 108±8 01 (04.54%)	325±7 14±5 101±5 00	314±5 12±4 106±6 00	-- -- -- --	
ECG changes Prolonged PR interval Qt interval QRS complex	 02 (09.09%) 02 (09.09%) 01 (04.54%)	 05 (21.73%) 04 (18.18%) 05 (22.72%)	 06 (26.08%) 04 (18.18%) 04 (18.18%)	 13 10 10	
No of patients with LV impairment Exercise induced AF Recurrence	 00 04 00	 00 02 00	 00 01 00	 00 07 00	
Deaths	0	0	0	00	--

Discussion

In this study 68 patients with AF were considered as per the inclusion criteria, exclusion criteria and divided into three groups and administered anti-arrhythmic drugs as per the approved protocol. There was no statistical significant difference in the age, gender, duration of AF prior to the study, recruitment period after initiating the anti-arrhythmic drugs, duration of follow up, side effects, deaths and the clinical categories of AF (Table 1) among the three groups. Flecainide alone has a tendency to cause an important pro-arrhythmic effect to convert AF to atrial flutter which occurred in 01 (04.54%) patient of group A (Flecainide alone). In a similar study by Crijns H.J., van Gelder I.C *et al* [19] and Boriani G., Diemberger I., *et al* [20] observed conversion to atrial flutter in their study was 3 to 5%. To prevent recurrences Flecainide had to be combined with beta blockers as a proven strategy and hence in this study Metoprolol was used to treat AF patients. Beta blockers are required to attain sinus rhythm. Capucci *et al*. [21] and Lewis G.P., Holtzman J.L *et al* [22] from their study have definitely proven that recurrences of AF could be prevented at one year follow up by combining Metoprolol with Flecainide; in this study patients were followed up for 21 months without any recurrences (Table 1). Digoxin can also be used as AV blocker to prevent recurrences but patients need to be monitored of serum digoxin concentrations as they were more likely to rise when used in combination with Flecainide [23]. Similarly combination of Flecainide and Verapamil could produce additive effects on the myocardial contractility [24]. Review of literature showed that Flecainide was useful in acute symptomatic AF patients to restore sinus rhythm with greater success rates than Propafenon and Amiodarone [25]. In the present study IV Flecainide was used in group A and C patients to control acute AF and obtain sinus rhythm. In the treatment of paroxysmal AF and Acute AF maintaining the sinus rhythm appears more advantageous than controlling only the heart rate [26]. Apart from Amiodarone which is used as a first line anti-arrhythmic drug to combat AF Flecainide seemed to be superior as the former has higher adverse effect rate and many patients tend to discontinue the treatment resulting in complications [27,28]. The mean duration past the diagnosis of patients with AF was 11.8±2.35 months with a variation of 11.6 to 12 months. There was statistical significant correlation between the three groups of patients with AF who were administered different anti-arrhythmic drug protocols; analyzed by Pearson R calculator.

The R value was 0.9998 and the p value was 0.0001 (p taken as significant at <0.05). There was also correlation between Flecainide (group A) and Flecainide and Metoprolol (group B) and also between Group B and C in this study. (The p value was 0.00001 in both the correlations). There were no recurrences or deaths in any of the three groups. There were exercise induced AF in all the three groups (04 in group A, 02 in Group B and 01 in Group C), (Table1). Remaining 20 (86.36%), 22 (91.30%) and 2295.65%) patients of Groups A, B and C respectively, obtained sinus rhythm during their follow up examinations over the period of two years of the study. In a similar study by Capucci A, Piangerelli L, Ricciotti J, Gabrielli D *et al*, (19) showed that flecainide and metoprolol combination reduced significantly the AF recurrences by the end of 1 year compared to Flecainide alone in their subjects (66.7 vs. 46.8%; p < 0.001) and also showed improvement in patients with persistent AF (71.1 vs. 43.6%; P = 0.025). But they found no improvement in the subjects when Metoprolol (beta-blocker therapy) was added in addition to flecainide. A similar study by Wang G, Zhao N, Zhong S, Wang Y, Li J. [29] the authors reported Flecainide therapy was superior to standard therapy in reducing the risk of arrhythmic events and exercise induced arrhythmia score in patients with AF, (p value 0.00001 and 0.03 respectively). They also pointed out that combination therapy with Flecainide and beta blockers was superior to beta blocker therapy alone in reducing the symptoms and arrhythmic recurrences in AF patients (p values- 0.0003 and 0.005). They commented that Flecainide had no adverse effects or increased risk when compared to beta blockers alone. No deaths were reported from their study when Flecainide was used.

Conclusions

Flecainide was found to be a safe, effective anti-arrhythmic drug which could be used as a monotherapy or in combination with Metoprolol with low side effects and no mortality. Combination therapy with Metoprolol gave an added advantage of controlling the heart rate both at rest and at exercise and preventing exercise induced arrhythmias. Metoprolol therapy alone was correlating with the Flecainide alone and Flecainide and Metoprolol combination therapy but obtaining sinus rhythm superior with the later. Many more randomized clinical trials should be conducted to develop a protocol in the management of paroxysmal, acute and remission types of Atrial Fibrillation.

References

1. Chugh S.S., Havmoeller R., Narayanan K., *et al*. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. Circulation. 2014; 129:837–847.
2. Tegene E., Tadesse I., Markos Y., *et al*. Prevalence and risk factors for atrial fibrillation and its anticoagulant requirement in adults aged ≥40 in jimma town, southwest ethiopia: a community based cross-sectional study. Int j cardiol heart vasc. 2019; 22:199–204.
3. Saggu D.K., Sundar G., Nair S.G., *et al*. Prevalence of atrial fibrillation in an urban population in india: the nagpur pilot study. Heart asia. 2016; 8:56–569.
4. Soni A., Karna S., Fahey N., *et al*. Age-and-sex stratified prevalence of atrial fibrillation in rural western india: results of smart-india, a population-based screening study. Int j cardiol. 2019;280: 84–88.
5. Jan Heeringa, Deirdre A, M. Van Der Kuip *et al*. Prevalence, incidence and lifetime risk of atrial fibrillation: the rotterdam study, eur heart j; 27: 949–953.
6. Saggu Dk, Rangaswamy Vv, Yalagudri S, Sundar G, Reddy NK, Shah V, K K, Shankar M, Chennapragada S, Narasimhan C. Prevalence, clinical

profile, and stroke risk of atrial fibrillation in rural Andhra Pradesh, India (the AP-AF study). Indian Heart J. 2022 Mar-Apr;74(2):86-90.
7. Lip GYH, Beevers D G, Singh S P, Watson R D S. ABC of Atrial Fibrillation: Aetiology, Pathophysiology and Clinical Features BMJ. 1995; 311: 1425.
8. Rillig A, Magnussen C, Ozga AK, *et al*. Early Rhythm Control Therapy in Patients With Atrial Fibrillation and Heart Failure. Circulation 2021; Jul 30: [Epub ahead of print].
9. Della Rocca D.G., Mohanty S., Trivedi C., Biase L.D., Natale A. Percutaneous Treatment of Non-Paroxysmal Atrial Fibrillation: A Paradigm Shift from Pulmonary Vein to Non-Pulmonary Vein Trigger Ablation? Arrhythm. Electrophysiol. Rev. 2018; 7:256.
10. Allen LaPointe N.M., Dai D., Thomas L., Piccini J.P., Peterson E.D., Al-Khatib S.M. Comparisons of Hospitalization Rates Among Younger Atrial Fibrillation Patients Receiving Different Antiarrhythmic Drugs. Circ. Cardiovasc. Qual. Outcomes. 2015; 8:292–300.
11. Echt D.S., Liebson P.R., Mitchell L.B., Peters R.W., Obias-Manno D., Barker A.H., Arensberg D., Baker A., Friedman L., Greene H.L., *et al.* Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo: The Cardiac Arrhythmia Suppression Trial. N. Engl. J. Med. 1991; 324:781–788.
12. Holmes B., Heel R.C. Flecainide A Preliminary Review of Its Pharmacodynamic Properties and Therapeutic Efficacy. Drugs. 1985; 29:1–33.
13. Anno T., Hondeghem L.M. Interactions of Flecainide with Guinea Pig Cardiac Sodium Channels. Importance of Activation Unblocking to the Voltage Dependence of Recovery. Circ. Res. 1990;66:789–803.
14. Mehra D., Imtiaz M.S., van Helden D.F., Knollmann B.C., Laver D.R. Multiple Modes of Ryanodine Receptor 2 Inhibition by Flecainide. Mol. Pharm. 2014; 86:696.
15. Tarantino N., Della Rocca D.G., De Leon De La Cruz N.S., Manheimer E.D., Magnocavallo M., Lavalle C., Gianni C., Mohanty S., Trivedi C., Al-Ahmad A., *et al*. Catheter Ablation of Life-Threatening Ventricular Arrhythmias in Athletes. Medicina. 2021; 57:205.
16. Farshi, R, Kistner, D, Sarma, JS. "Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five drug regimens". J Am Coll Cardiol. 1999; 33: 304-06.
17. Fuster, V, Ryden, LE, Cannom, DS. "2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines". Circulation. 2011:123: 269-367.
18. Helfand M, Peterson K, Christensen V, Dana T, Thakurta S. Drug Class Review: Beta Adrenergic Blockers: Final Report Update 4 [Internet]. Oregon Health & Science University; Portland (OR): Jul, 2009.
19. Capucci A, Piangerelli L, Ricciotti J, Gabrielli D, Guerra F. Flecainide-metoprolol combination reduces atrial fibrillation clinical recurrences and improves tolerability at 1-year follow-up in persistent symptomatic atrial fibrillation. Europace. 2016 Nov; 18(11):1698-1704.
20. Crijns H.J., van Gelder I.C., Lie K.I. Supraventricular Tachycardia Mimicking Ventricular Tachycardia during

Flecainide Treatment. Am. J. Cardiol. 1988; 62:1303–1306.
21. Boriani G., Diemberger I., Biffi M., Martignani C., Branzi A. Pharmacological Cardioversion of Atrial Fibrillation: Current Management and Treatment Options. Drugs. 2004; 64:2741–2762.
22. Lewis G.P., Holtzman J.L. Interaction of Flecainide with Digoxin and Propranolol. Am. J. Cardiol. 1984;53: B52–B57.
23. Trujillo T.C., Nolan P.E. Antiarrhythmic Agents: Drug Interactions of Clinical Significance. Drug Saf. 2000; 23:509–532.
24. Holtzman J.L., Finley D., Mottonen L., Berry D.A., Ekholm B.P., Kvam D.C., McQuinn R.L., Miller A.M. The Pharmacodynamic and Pharmacokinetic Interaction between Single Doses of Flecainide Acetate and Verapamil: Effects on Cardiac Function and Drug Clearance. Clin. Pharm. 1989; 46:26–32.
25. Romano S., Fattore L., Toscano G., Corsini F., Coppo A., Catanzaro M., Romano A., Martone A., Caccavale F., Iodice E., *et al*. Effectiveness and side effects of the treatment with propafenone and flecainide for recent-onset atrial fibrillation. Ital. Heart J. Suppl. 2001; 2:41–45.
26. Khan I.A. Oral Loading Single Dose Flecainide for Pharmacological Cardioversion of Recent-Onset Atrial Fibrillation. Int. J. Cardiol. 2003; 87:121–128.
27. Della Rocca D.G., Mohanty S., Mohanty P., Trivedi C., Gianni C., Al-Ahmad A., Burkhardt J.D., Gallinghouse G.J., Hranitzky P., Sanchez J.E., *et al*. Long-term Outcomes of Catheter Ablation in Patients with Longstanding Persistent Atrial Fibrillation Lasting Less than 2 Years. J. Cardiovasc. Electrophysiol. 2018; 29:1607–1615.
28. Mohanty S., Trivedi C., Gianni C., Della Rocca D.G., Morris E.H., Burkhardt J.D., Sanchez J.E., Horton R., Gallinghouse G.J., Hongo R., *et al*. Procedural Findings and Ablation Outcome in Patients with Atrial Fibrillation Referred after Two or More Failed Catheter Ablations. J. Cardiovasc. Electrophysiol. 2017; 28:1379–1386.
29. Wang G, Zhao N, Zhong S, Wang Y, Li J. Safety and efficacy of flecainide for patients with catecholaminergic polymorphic ventricular tachycardia: A systematic review and meta-analysis. Medicine (Baltimore). 2019 Aug;98(34):e16961.