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THERAPEUTIC POTENTIAL OF FLECAINIDE FOR CARDIAC ARRHYTHMIAS: A SHORT REVIEW OF STUDIES AND CLINICAL RECOMMENDATIONS

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Flecainide is a IC antiarrhythmic drug with a history of more than 30 years, nowadays it is widely used for the management of acute episodes of atrial fibrillation and sinus rhythm maintenance, however, firstly was approved for the treatment of ventricular arrhythmia and later due to the results of the Cardiac Arrhythmia Suppression Trial was contraindicated in patients with ischemic structural heart disease. Of note, flecainide use is feasible in different clinical situations, such as catecholaminergic polymorphic ventricular tachycardia, for unmasking Brugada syndrome, and for patients with long QT syndrome. In our country, flecainide is new for clinical use; therefore, the clinical experience with flecainide is limited. In this review article, we aim to describe the use of flecainide and its role in the management of cardiac arrhythmias.

Key words: flecainide; class IC antiarrhythmic drug; ventricular arrhythmias; atrial fibrillation

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In the era of widespread availability of catheter ablation of arrhythmias, antiarrhythmic drugs remain the cornerstone of therapy and maintenance of sinus rhythm [1, 2]. Among the IC class antiarrhythmic drugs, flecainide a drug developed in the 70s and later approved for use in a number of countries in the 1980s [3], is an antiarrhythmic agent mainly used for the prevention of atrial fibrillation (AF) recurrent episodes, ventricular arrhythmias in some categories of patients, as well as for termination and prevention of recurrence of supraventricular tachycardia (SVT). Although flecainide has a long history and has been studied in a number of clinical trials for a wide range of heart rhythm disturbances [4-7], its market availability has been limited to some countries. Over the past few years, the geography of the drug's presence has significantly expanded [8], and in 2024, flecainide became available in Russia, expanding the possibilities of drug therapy for patients. However, it remains a new drug for health care practitioners (Fig. 1). This review article presents the results of some recent studies on the use of flecainide in the treatment of cardiac arrhythmias.

BASIC DATA ON PHARMACOKINETICS AND PHARMACODYNAMICS

When taken orally, flecainide is well absorbed, its bioavailability is 90-95%, it does not undergo significant systemic metabolism in the liver. Flecainide binds to plasma proteins by 32-58%, passes through the placenta and is excreted in breast milk. Flecainide is intensively metabolized by the cytochrome P450 CYP2D6 isoenzyme. Flecainide and its metabolites are excreted mainly in the urine, only 5% of the administered dose is excreted with faeces [9]. The rate of excretion of flecainide decreases with renal insufficiency, liver diseases, heart failure and with a pH increase in urine (alkalinization). The half-life is 12-27 hours [10].

Flecainide binds to the sodium channels of cardiomyocyte membranes, causing a powerful slowdown in the conduction of cardiac impulse and suppression of spontaneous ventricular extrasystoles. Flecainide binds strongly to fast sodium channels and, thus, slows down the rate of depolarization and reduces conduction in the atria, atrioventricular node, ventricles and Purkinje fibers. The most pronounced effect is observed in Purkinje fibers. Flecainide also increases the refractoriness of anterograde-conducting and, especially, retrograde-conducting accessory atrioventricular pathways [11]. On an ECG, the effect of flecainide is manifested by a prolongation of the PR interval and an expansion of the QRS complex, which may be accompanied by a prolongation of the QT interval. The effect on the JT interval is insignificant [12]. Flecainide usually has no effect on heart rate. Flecainide intake may be accompanied by a decrease in left ventricular ejection fraction due to a negative inotropic effect [13].

ATRIAL FIBRILLATION

Atrial fibrillation termination

In accordance with the Guidelines for the diagnosis and management of AF of the European Society of Car-

diology (ESC) 2020, the use of flecainide is indicated in patients without significant left ventricular hypertrophy, systolic left ventricular dysfunction or coronary heart disease for conversion to sinus rhythm [14]. Flecainide can be used orally (including "pill in the pocket"), or intravenously, which leads to a rapid (3-5 hours) restoration into sinus rhythm in >50% of patients (51% after 3 hours, 72% after 8 hours). In addition, it is advisable to simultaneously prescribe a drug that slows down atrioventricular conduction to prevent the transformation of AF into atrial flutter with conduction 1:1 to the ventricles. Sinus rhythm restoration with intravenous flecainide usually requires hospitalization and medical supervision. Oral administration only requires medical control. To date, a series of studies has been published estimating the time to restore the sinus rhythm in AF after administration of flecainide.

In a randomized study by G.Boriani et al., flecainide was used to convert recent AF (<48 hours) [15]. Four hundred and seventeen patients without heart failure were hospitalized and randomized to the following groups: (1) placebo in 121 patients; (2) intravenous amiodarone at a dose of 5 mg/kg bolus, followed by 1.8 g/24 hours in 51 patients; (3) propafenone intravenously, 2 mg/kg bolus, for 0.0078 mg/kg/min in 57 patients; (4) propafenone orally, 600 mg orally once in 119 patients; (5) flecainide 300 mg orally once in 69 patients. Interestingly, in the placebo group, recovery of sinus rhythm within 8 hours was observed in 37% of patients, in the amiodarone group, the frequency of conversion, although higher, did not significantly differ from the placebo group (57%). In the flecainide and propafenone groups, the frequency of AF conversion was maximal and comparable (about 75%).

In another prospective single-blind study, 150 patients with symptomatic recent AF (duration ≤48 hours) were randomized into the following groups: intravenous administration of flecainide, propafenone or amiodarone. Flecainide and propafenone were administered as a bolus dose of 2 mg/kg for 20 minutes [16]. A second bolus dose of 1 mg/kg was administered for 20 minutes if AF conversion was not achieved within 8 hours. Amiodarone was administered as a bolus of 5 mg/kg for 20 minutes, followed by a continuous infusion of 50 mg/hour. By the end of the 12-hour follow-up period, AF conversion was achieved in 45 patients (90%) in the flecainide group, 36 (72%) in the propafenone group and 32 (64%) in the amiodarone group (p=0.008 for general comparison, p=0.002 for flecainide versus amiodarone, p=0.022 for flecainide versus propafenone and p=0.39 for propafenone versus amiodarone). The median time to conversion to sinus rhythm was shorter in the group of flecainide (25 minutes; range from 4 to 660) and propafenone (30 minutes; range from 10 to 660) than in the group of amiodarone (333 minutes; range from 15 to 710; p<0.001). Flecainide was more effective than propafenone and amiodarone for the conversion of recent AF.

In the study of A.Kartalis et al., flecainide was administered intravenously in combination with oral beta blockers for termination of recent AF paroxysm (≤48 hours): in 121 patients (73 men and 48 women with an average age of 61.4 years), conversion to sinus rhythm within 2 hours was observed in 99 patients (81.8%), and the average time to AF treatment was 11.7 minutes (from 3 to 23 minutes). The authors noted that this conversion time was the shortest in comparison with other studies and may probably be associated with the concomitant use of beta blockers [17]. No serious side effects were reported in the study.

In 2022, H.J.G.M.Crijns et al. presented the results of an open multicenter study using a new inhaled form of flecainide [18]. 101 patients with symptomatic AF were included (the duration of the AF episode was less than 48 hours), inhalation of a solution of flecanide acetate using a nebulizer was performed independently (30 mg [n=10], 60 mg [n=22], 90 mg [n=21], 120 mg [n=19] and 120 mg in a compound containing saccharin [n=29]). To record the effects of the drug, continuous ECG recording was performed for 4 hours and the concentration of flecainide in blood plasma was evaluated. The rate of rhythm conversion and plasma concentration increased depending on the dosage, with the use of the highest dose in 48% of patients, conversion to sinus rhythm was observed within 90 minutes. Among patients with the maximum concentration of the drug in plasma (>200 ng/ml), the proportion of rhythm conversion within 90 minutes was 50%; at plasma concentrations <200 ng/ml, it was 24% to restore the rhythm. The median conversion time was 8.1 minutes. No significant cardiovascular side effects were reported, but transient cough, sore throat and throat irritation were present. This study showed that oral inhalation of flecainide is effective and safe for the conversion of AF to sinus rhythm.

The results of the second phase of this study were published in 2024. A dose of 120 mg was chosen for the conversion of AF in 90 patients. Sinus rhythm was restored in 48% of patients after inhalation for 90 minutes [19]. The total rate of rhythm conversion was 42.6% within 90 minutes after completion of inhalation, with the majority (75.0%) of conversions occurring within the first 30 minutes (median 14.6 minutes). It was also noted that the probability of conversion was significantly lower in patients with the presence of flecainide in plasma before inhalation

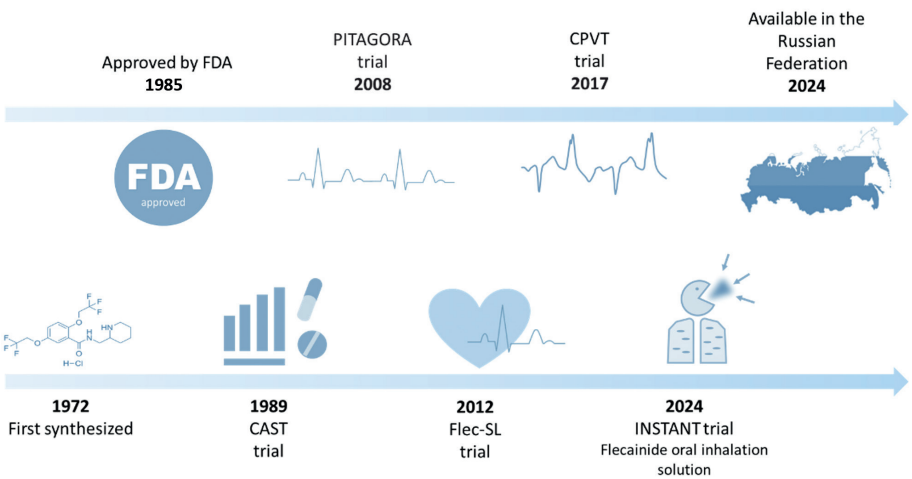

Figure 1. Timeline of introduction and research of flecainide

compared with those who had no previous intake of flecainide (15.3% and 46.9%, respectively).

Long-term suppression of atrial fibrillation recurrences

IC class antiarrhythmic drugs are recommended for long-term rhythm control in patients with AF without structural heart disease [20]. The last review of scientific data on the use of flecainide was published in 2019 by L.Valembois et al. [21]. This article is an update of previously published reviews from the Cochrane database in 2006, 2012 and 2015, analyzing four randomized controlled trials with a total of more than 500 patients. It has been shown that long-term use of flecainide is significantly more effective in preventing recurrent episodes of AF compared with the control (no treatment group or placebo group) with a relative risk of arrhythmia recurrence of 0.65.

In 2008, the PITAGORA's trial results were released, this was a prospective, randomized, single-blind study [22]. The aim of the study was to evaluate IC class antiarrhythmic drugs, propafenone and flecanide, in comparison with class III drugs (amiodarone or sotalol) as a prevention of AF recurrences in patients after pacemaker implantation. The primary endpoint was combined and included death, permanent AF, hospitalization for cardiovascular diseases, cardioversion for atrial arrhythmia, and a change of antiarrhythmic medication. A total of 176 patients (72±8 years old) from 27 medical institutions were recruited. Randomization was performed in a 3:2 ratio for a Class III or class IC drug, respectively. The dosages of oral drugs were as follows: 200 mg for flecainide, 450-600 mg for propafenone and 160-240 mg for sotalol. Amiodarone was prescribed at a dosage of 600 mg for 10 days, then 400 mg, after which a daily maintenance dose of 200 mg / day was used. The average follow-up period was 20±9 months. Comparing flecainide, propafenone and sotalol separately, only flecainide demonstrated a criterion of no less effectiveness with amiodarone with an absolute difference of -10.3% and 95% confidence interval between 5.4% and -25.9% (p=0.01). Freedom from the primary endpoint after 1 year was 68% for amiodarone, 77% for flecainide, 66% for sotalol and 72% for propafenone. One of the main limitations of this study was the small number of patients in each group, extrapolation of the results is limited to patients after pacemaker implantation and the absence of significant structural heart disease.

Another important study was the Flec-SL study, a prospective, randomized, open-label, blinded study involving 44 cardiac centers [23]. For this study, patients with persistent atrial fibrillation undergoing planned cardioversion were selected, after which randomization was carried out into one of two groups: the flecainide treatment group (200-300 mg/day) for 4 weeks (short term treatment), the flecainide treatment group for 6 months (long term treatment), and the control group. The primary endpoint was combined and included time to persistent AF or death. According to the results of a 4-week follow-up in 242 patients, in the flecainide group, the absence of a primary endpoint was observed in 70.2% of patients versus 52.5% in the control group (P=0.016). AF recurrences were observed in 120 (46%) of 261 patients receiving a short term, and in 103 (39%) of 263 patients receiving a long term of flecainide therapy. The authors concluded that a short term of flecainide therapy significantly reduces the risk of AF recurrence, while a long course shows better therapy results. It should be noted that these results are based on a limited observation period.

Antiarrhythmic therapy and catheter ablation of atrial fibrillation

In the era of catheter ablation treatment of AF patients, a long waiting time for the procedure can be a serious limitation and an important factor in the progression of the disease, given the ineffectiveness of antiarrhythmic drugs in this particular population [24].

A recent Canadian study estimated the time from referral for an ablation procedure to its completion [25]. An increase in waiting time from 211 days to 244 days was demonstrated compared to the previous register. One in five patients on the waiting list died, was hospitalized or received emergency care due to deterioration and the appearance/progression of heart failure. These adverse events were more often observed in patients on the waiting list with paroxysmal AF.

Another study showed that the time from diagnosis to ablation is a factor independently associated with recurrence of arrhythmia and the need for repeated ablation [26]. Perioperative treatment with antiarrhythmic drugs is important for maintaining sinus rhythm and maintaining the quality of life of patients, while optimal antiarrhythmic therapy before ablation remains poorly understood [27].

According to the ERHA-ESC registry in the Russian population, class IC antiarrhythmic drugs are received by 28% of patients before pulmonary vein isolation, whereas class III antiarrhythmic drugs are received by 53% [28]. Given the emergence of new drugs for use in AF, in the near future it is likely that the established regimens of preoperative and postoperative therapy of patients with indications for catheter ablation of AF will change.

VENTRICULAR ARRHYTHMIAS

Since 1984, flecainide has been widely used to treat not only AF, but also other cardiac arrhythmias. In observational studies, high efficacy of suppression of ventricular tachyarrhythmias has been demonstrated. However, in 1991, the results of the CAST study were presented and shown that the use of flecainide in patients with reduced ejection fraction and frequent ventricular extrasystoles after myocardial infarction was associated with a high incidence of adverse events and death [4]. As a result, the use of flecainide in ventricular arrhythmias was limited to certain groups of patients where the proarrhythmogenic risk of its use is minimal.

Catecholaminergic polymorphic ventricular tachycardia

In 2023, A.T.Bergeman et al., published the results of a multicenter case cross-over study evaluating the possibilities of flecainide in reducing the number of arrhythmic events in addition to initial beta blocker therapy for catecholaminergic polymorphic ventricular tachycardia (CPVT) [29]. This study included 247 patients (who received an average dose of flecainide 2.2 mg/kg per day). Initially, all patients received a beta-adrenoblocker, 70 (28%) had previously had a cardioverter defibrillator implanted, and 21 (9%) under-

went left-sided sympathetic cardiac denervation. Prior to the start of flecainide administration (median period 2.1 years), 41 patients (17%) had 58 episodes of ventricular tachycardia (VT). After the start of flecainide therapy (median follow-up of 2.9 years), 38 VT episodes were registered in 23 patients (9%). Thus, the authors suggested that combination therapy with flecainide with beta blockers is associated with a decrease in the frequency of ventricular arrhythmias. In other studies, flecainide has been proposed as monotherapy in patients with CPVT with poor tolerance of beta blockers. G.J.Padfield et al. described a series of cases when flecainide was better tolerated by patients, and its administration was associated with a tendency to increase heart rate and increase exercise tolerance [30].

Long QT syndrome

E.Chorin et al., evaluated the long-term safety and efficacy of flecainide therapy in patients with long QT syndrome (LQTS) type 3 with the D1790G SCN5A mutation. This study included 30 patients treated with flecainide and followed up for 1-215 months (on average, 145±54 months, median 140 months). During flecainide therapy, QTc decreased significantly, by an average of 53 ms (10%; P <0.01). QTc shortening was associated with clinical improvement: all patients who were committed to the prescribed therapy had no arrhythmic events for 83±73 months. 6 out of 20 patients who stopped taking flecainide had arrhythmic events after 1-11 months. An important finding of the work was that in 6 patients, initiation of flecainide therapy led to the appearance of Brugada-like changes on the ECG. Despite such limitations as the lack of monitoring of plasma flecainide levels and incomplete adherence to treatment, the results of the study indicated the possibility of using flecainide in patients with LQTS carrying the D1790G SCN5A mutation [31].

Brugada syndrome

Some researchers have used flecainide for oral or intravenous administration to diagnose ("unmask") Brugada syndrome. In 2005, C.Wolpert et al. compared the capabilities of intravenous flecainide and ajmaline in provoking the ECG pattern of Brugada syndrome [32]. 22 patients were included, in all of them, the administration of ajmaline at a dose of 1 mg/kg of body weight for 10 minutes provoked or increased ST segment elevation in the right thoracic leads. When flecainide was administered at a dose of 2.0 mg/kg of body weight (maximum 150 mg) for 10 minutes, the provocative test turned out to be positive in only 15 out of 22 patients. Despite the probably lower effectiveness of flecainide in the diagnosis of Brugada syndrome, its use may be justified if ajmaline is unavailable.

The use of oral flecainide at a dose of 400 mg in order to provoke Brugada-like ECG changes has been described in separate observations. In 2022, the results of the use of a low dose of oral flecainide for the diagnosis of Brugada syndrome were published: 30 minutes after taking 300 mg of flecainide, ECG changes characteristic of type 1 Brugada syndrome were detected in 2 patients [6]. At the same time, the maximum manifestations on the ECG were detected after 3-4 hours.

Other channelopathies

The use of flecainide has been tested in patients with Andersen-Tawil syndrome, a rare genetic disease characterized by frequent ventricular tachyarrhythmias (bidirectional ventricular tachycardia), dysmorphic disorders and periodic paralysis. K.Miyamoto et al. evaluated the efficacy of flecainide in ventricular arrhythmias in patients with Andersen-Tawil syndrome with the KCNJ2 mutation [33]. The study included 10 patients, all of whom had previously registered bidirectional ventricular tachycardia, despite the use of beta blockers. Holter monitoring and stress test were performed initially and after oral administration of flecainide (150±46 mg/day). Flecainide reduced the number of episodes of ventricular arrhythmia from 38407±19956 to 11196±14773 per day. In patients with stress-induced unstable ventricular tachycardia, the use of flecainide suppressed episodes of arrhythmia. During the average therapy period of 23±11 months, none of the patients had syncope or cardiac arrest. The authors suggested that oral flecainide therapy is effective for suppressing ventricular arrhythmia in Andersen-Tawil syndrome.

CLINICAL RECOMMENDATIONS

Since flecainide was registered for clinical use in Russia only in April 2024, it is not mentioned in the current clinical guidelines for the management of patients with ventricular arrhythmias [34], atrial fibrillation [20] and supraventricular tachycardia [35], approved by the expert council of the Ministry of Health in 2020.

At the same time, according to the recommendations of the European Society of Cardiology 2020 on the management of patients with AF, the possible use of flecainide (along with some other IC class drugs) is indicated in the following situations: for pharmacological cardioversion of recently onset AF (excluding patients with severe structural heart disease); for long-term rhythm control in patients with AF with normal left ventricular function and without structural heart disease, including significant left ventricular hypertrophy and myocardial ischemia; as a preliminary therapy to increase the success of electrical cardioversion in AF; in some cases, with infrequent episodes of recent AF in persons without significant structural or ischemic heart disease - in the form of a single continuous oral administration ("pill in the pocket") for cardioversion, but only after a preliminary evaluation of the effectiveness and safety of the drug in a particular patient. Concomitant use of flecainide with a drug that slows down the atrioventricular node conduction (with good tolerability) is advisable [36].

According to the guidelines of the ESC 2022 on the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death [37], flecainide can be used to suppress idiopathic ventricular arrhythmias (extrasystoles and ventricular tachycardia). It is also recommended to consider flecainide therapy when catheter ablation of the arrhythmia substrate is unavailable, undesirable or especially risky in patients with symptomatic idiopathic ventricular arrhythmias from the right ventricular outflow tract and left ventricular fascicular arrhythmias. The recommendations include the use of flecainide in Andersen-Tawil syndrome and CPVT. Flecainide can be used to relieve monomorphic ventricular tachycardia without impaired hemodynamics in patients without structural myocardial diseases.

CONCLUSION

Flecainide is an important member of the IC class antiarrhythmic drugs family for clinical use, having the ability to terminate AF and restore sinus rhythm, prevent recurrence of AF and ventricular arrhythmias in the absence of structural heart diseases, in some channelopathies, as well as a diagnostic tool for Brugada syndrome.

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