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Antiarrhythmic therapy in patients with atrial fibrillation

Leczenie antyarytmiczne chorych z migotaniem przedsionków

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Key words
atrial fibrillation, antiarrhythmic drugs

Słowa kluczowe
migotanie przedsionków,
leki antyarytmiczne

S u m m a r y

Atrial fibrillation is the most frequent arrhythmia, that still remains one of the most difficult to pharmacological management. Antiarrhythmic drugs have been widely used to restore sinus rhythm and to prevent reccurence of arrhythmia, but pharmacological therapy is limited to several available agents, because of insufficient efficiacy and the significant risk of serious adverse effects. In patients with atrial fibrillation without structural heart disease, it is possible to perform pharmacological cardioversion due to flekainid, propafenon, ibutilid or vernakalant administration, but in patients with structural heart disease, there is possible only amiodarone using. Long-lasting antiarrhythmic therapy increases not only probability of the sinus rhythm maintainig, but also the risk of adverse side effects occuring. The key problem determines a choice between the rhythm control strategy or the rate control in patients with sustained atrial fibrillation. Recently, also it has been emphasized upstream therapy importance. There is a lot of expectations reffering to reaserches aimed at introducing new antiarrhythmic drugs with favorable efficiacy and safety profile. However, despite undoubted development of clinical and experimental pharmacology and cardiology, antiarrhythmic drug therapy of atrial fibrillation remains an important challenge.

S t r e s z c z e n i e

Migotanie przedsionków pozostaje najczęściej występującą, lecz jedną z najtrudniej poddających się leczeniu farmakologicznemu arytmią. Leki antyarytmiczne służą przywróceniu rytmu zatokowego oraz zapobieganiu nawrotom arytmii, ale leczenie farmakologiczne ogranicza się do kilku dostępnych preparatów ze względu na niewystarczającą skuteczność terapii oraz poważne działania niepożądane. U pacjentów z migotaniem przedsionków bez strukturalnej choroby serca można przeprowadzić kardiowersję farmakologiczną podając flekainid, propafenon, ibutylid lub wernakalant, u chorych ze strukturalną chorobą serca, możliwe jest zastosowanie wyłącznie amiodaronu. Przewlekłe leczenie antyarytmiczne zwiększa nie tylko prawdopodobieństwo utrzymania rytmu zatokowego, ale również ryzyko wystąpienia niekorzystnych objawów ubocznych. Kluczowym problemem pozostaje wybór pomiędzy strategią przywrócenia i utrzymywania rytmu zatokowego, a pozostawieniem utrwalonego migotania przedsionków i optymalizacją kontroli częstości rytmu komór. Ostatnio podkreśla się również znaczenie leczenia wspomagającego. Wiele oczekiwań wiąże się z badaniami mającymi na celu wprowadzenie nowych leków antyarytmicznych o korzystnym profilu skuteczności i bezpieczeństwa. Jednak pomimo niewątpliwego rozwoju kardiologii i farmakologii zarówno doświadczalnej, jak i klinicznej, leczenie migotania przedsionków wciąż stanowi poważne wyzwanie.

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INTRODUCTION

Although, atrial fibrillation (AF) is the most common arrhythmia occurring in general population, incomplete knowledge of the etiology and complexity of the previously known causes of atrial fibrillation makes it still one of the most difficult arrhythmias to treat. Factors responsible for the occurrence of atrial fibrillation and necessary for its perpetuation were presented by a well-known French electrophysiologist Coumel in the form of a triangle (fig. 1) (1). Removal or modification of many described factors allows for an arrhythmia elimination, and if this is not possible, a lot of targets for the use of drug therapy can be found.

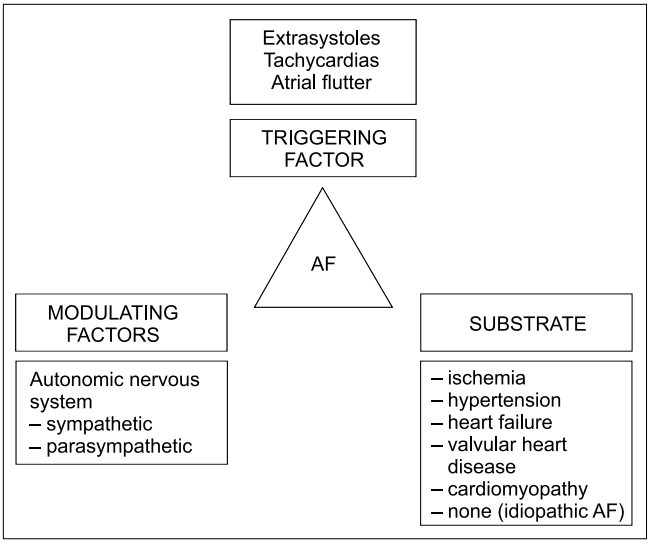

Fig. 1. Coumel's triangle – factors influencing the onset and maintenance of atrial fibrillation.

First attempts to found an effective drug preventing the occurrence of atrial fibrillation date back to the first description of arrhythmia in animals presented by William Harvey in 1628 and to the observations, made in subsequent years, which revealed that the incidence of irregular pulse in patients is associated with unfavourable prognosis. In 1785 the beneficial effects of digitalis in patients with heart failure were described, and a quinidine (2), which was introduced for the treatment of AF in the nineteenth century, is considered to be the first typical antiarrhythmic drug. In subsequent years, next antiarrhythmic drugs were synthesized and introduced into clinical practice and their classification made in 1969 by Vaughan Williams after a few modifications it is still used today (tab. 1) (3).

Table 1. Vaughan-Williams Classification of Antiarrhythmic Drugs (3).

Class IA	disopyramide, procainamide, quinidine
Class IB	lidocaine, mexiletine
Class IC	flecainide, propafenone
Class II	beta-blockers
Class III	amiodarone, dofetilide, ibutilide, sotalol
Class IV	non-dihydropyridine blockers of calcium channels (verapamil, diltiazem)

For the present, there is no perfect drug, allowing for prevention of atrial fibrillation occurrence and for effective maintenance of sinus rhythm. List of antiarrhythmic drugs recommended for use in patients with atrial fibrillation rather shortens than lengthens. This particularly concerns IA class drugs (quinidine and disopyramidum), which are characterized by potential pro-arrhythmic effect (risk of QT prolongation and the occurrence of torsade de pointes type ventricular tachycardia) and IC class, contributing by their pro-arrhythmic potential especially in patients with heart failure, to unfavorable prognosis, as it was demonstrated in the CAST study published in 1989 and evaluating the efficacy of moricizine, encainide and flecainide in patients after myocardial infarction, with reduced ejection fraction and ventricular extrasystoles (4).

In currently available guidelines of the European Society of Cardiology concerning the treatment of patients with atrial fibrillation, published in 2010 and updated in 2012, antiarrhythmic drugs were divided into drugs used to restore sinus rhythm and drugs used for long – term sinus rhythm maintaining (5, 6).

DRUGS USED TO RESTORE SINUS RHYTHM

In patients with atrial fibrillation of recent onset (< 48 hours), for whom the strategy for maintaining sinus rhythm was chosen or for whom other medical indications for the restoration of sinus rhythm exist (for example, clinical symptoms persisting despite adequate control of ventricular rate), it is possible to carry out pharmacological cardioversion by administration of antiarrhythmic drug as an intravenous bolus. According to the current ESC guidelines in the first class of recommendations for patients in whom pharmacological cardioversion is preferred and there is no structural heart disease, an intravenously flecainide, propafenone, ibutilide or vernakalant should be used and in patients with structural heart disease an amiodarone should be used. ESC experts emphasize the need for continous medical supervision and electrocardiogram monitoring during and directly after intravenous drug administration because of the risk of ventricular arrhythmias, sinus arrest or atrioventricular block. In selected patients with atrial fibrillation of recent onset and without significant structural heart disease, according to the ESC guidelines, an outpatient pharmacological cardioversion by oral administration of high single dose of flecainide or propafenone (IIa class of recommendations) should be considered. The “pill-in-the-pocket” approach and pharmacological outpatient self-cardioversion is possible, if its safety was previously demonstrated in the hospital. It should be offered to patients suffering from severe symptoms of AF, with infrequent reccurence of arrhythmia and after the careful consideration all the indications and contraindications for the use of these drugs. Both flecainide and propafenone belong to Vaughan Williams Ic class and act by inhibiting the intracellular fast sodium current and slowing the conduction. Furthermore, flecainide inhibits the opening of potassium channels, particularly fast current component K (I_{Kr}), extending the action potential duration in atria and ventricles cells. In contrast, within the Purkinje fibers, flecainide shortens the action potential duration due to an inhibition of the Na channel. Recent studies suggest that flecainide also blocks the opening of ryanodine receptor (RyR), thus reducing the spontaneous calcium release from the sarcoplasmic reticulum, which can potentially cause late depolarization and triggered activity (7). Due to weak blocking of beta – adrenergic receptors propafenone should not be administered to patients with severe obstructive lung disease. IC class drugs are discouraged in patients with significant structural heart disease, as they may prolong the QT interval and widen QRS complexes, creating the risk of ventricular proarrhythmia, as well as unintentionally accelerate the ventricular fibril-

lation due to conversion of atrial fibrillation to atrial flutter with ventricular conduction 1:1. Described percentage of this type of pro-arrhythmic action of flecainide vary from 3.5 to 5.0% (8). In order to reduce the risk of rapid conduction of supraventricular arrhythmia to ventricles, along with propafenone or flecainide there should be administered drugs that inhibit atrioventricular conduction (for example, beta-blockers, verapamil or diltiazem). However, in one study it was demonstrated that propafenone and flecainide can be safely taken in outpatient cardioversion (1/569 episode of converting to atrial flutter with rapid ventricular rhythm), and their effectiveness is quite high (94%). The return of sinus rhythm after oral administration of propafenone (450-600 mg) and flecainide (200-300 mg) was observed after 2-6 hours (9). In a recently performed large randomized FLEC-SL study the efficacy of oral flecainide therapy for prevention of atrial fibrillation recurrence was proved. It has been shown that a short-term (4 weeks) treatment with flecainide after the conversion to sinus rhythm in patients with persistent atrial fibrillation is not worse than the long-term treatment (6 months), and the drug is more efficient than placebo (10).

Vernakalant is a drug, which has been used to pharmacological cardioversion in patients with atrial fibrillation of recent onset (IA class of recommendations), patients with atrial fibrillation with a duration time < 7 days and with moderate structural heart disease or < 3 days after cardiac surgery (IIb class of recommendation, level of evidence B). The drug acts mainly in the atria, inhibiting several ion channels and leading to a prolongation of refraction and the slowing of conduction in the atria. The influence of vernakalant on conduction in the ventricles is limited. The efficacy of this drug was evaluated in several clinical studies. In ACT study (I-IV, a medium-sized randomized placebo-controlled studies) it was demonstrated the superiority of vernakalant in comparison with placebo in restoring sinus rhythm in patients with atrial fibrillation lasting < 7 days. In the CRAFT study the efficacy of different vernakalant doses restoring sinus rhythm were evaluated, showing the percentage of conversion of AF to sinus rhythm of 61% with a vernakalant dosage of 2 mg/kg for the first dose + 3 mg/kg in the next dose. In ACT, AVRO and Scene2 studies an infusion of 1 mg/kg within 10 minutes was administered, and then a bolus of 2 mg/kg, if AF was present 15 minutes after the first infusion. In the majority of patients (75-82%), sinus rhythm returned after the first dose (11-13). In a direct comparison (AVRO study) vernakalant more effectively than amiodarone restored sinus rhythm after 90 minutes (51.7 vs 5.2%; $p < 0.0001$) and 4 hours after infusion (54.4 vs 22.6%; $p < 0.0001$).

In the subgroups of patients with cardiovascular diseases (coronary heart disease, including myocardial infarction or hypertension) the efficacy of the drug was similar to the control group (45.7 vs 47.3%), and the incidence of adverse events (blood pressure decrease, bradycardia or ventricular arrhythmia) did not increase significantly, with the exception of patients with heart failure, which were less likely to benefit from the drug. As was proved, vernakalant is ineffective in restoring sinus rhythm in patients with atrial fibrillation lasting more than 7 days and in patients with atrial flutter (14, 15). Among the significant adverse events observed in patients, who were treated with vernakalant, compared with patients receiving placebo, the most commonly observed (5-7%) were transient hypotension, bradycardia, which, however, did not cause the need of drug withdrawal and short nsVT episodes, were the most commonly observed (7.3 vs 1.6% in the placebo group). Adverse effects more often occured in patients with the heart failure, but in spite of QTc prolongation (from 20 to 25 msec), there was no arrhythmia of torsade de pointes type. Mentioning the above-cited clinical studies, ESC experts in the current guidelines have formulated recommendations to use vernakalant, as safe and effective agent in patients with minimal or moderate heart disease, but a special caution was recommended in patients with heart failure I and II NYHA class, due to the increased risk of hypotension and ventricular arrhythmias. Contraindications to the use of vernakalant involve: systolic blood pressure < 100 mmHg, acute coronary syndrome within the previous 30 days, severe heart failure in III and IV NYHA class and significant aortic stenosis.

In patients with AF of recent onset and structural heart disease the only drug that can be administered for pharmacological cardioversion is amiodarone (IA class of recommendations). Sinus rhythm after intravenous injection of amiodarone was able to restore within 24 hours in 80-90% of patients in comparison with return of sinus rhythm in 40-60% of subjects treated with placebo. Amiodarone does not act effectively in a short period of time after administration. According to the guidelines, for pharmacological cardioversion there should not be used drugs ineffective in converting recent onset AF to sinus rhythm in patients with atrial fibrillation. ESC experts included to this group: digoxin, verapamil, metoprolol and other beta-blockers and ajmaline (III class of recommendations).

In Polish conditions, only propafenone and amiodarone are the drugs commonly available in clinical practice. In many centers the drug commonly used to restore sinus rhythm is phenazolinum, which does not have place in the current ESC guidelines. Phenazolinum belongs to antihistamines (H1-receptor antagonist) with anti-allergic effect. Because of the anticholinergic and cell membrane stabilizing effects, phenazolinum is included to Vaughan Williams class IA drugs (similar to quinidine). The agent prolongs the duration and decreases the amplitude of the action potential and the resting potential of phase 4. The efficacy of phenazolinum in restoring sinus rhythm is estimated at 52-70% in comparison with the complete effectiveness of pharmacological cardioversion of approx. 62% (16). In the absence of a recommendation for the drug in current guidelines, phenazolinum use in restoring sinus rhythm should be treated with adequate reserve, albeit soon there will be published the results of a randomized study on the effectiveness of phenazolinum that may affect the justification for the increased use of the drug.

DRUGS USED TO MAINTAIN SINUS RHYTHM

Initiation of treatment aimed at maintaining sinus rhythm should be justified by the presence of persistent symptoms associated with atrial fibrillation episodes in patient. The updated guidelines on atrial fibrillation, taking into account the results of meta-analyzes and review papers confirming the efficacy of antiarrhythmic therapy, as well as emerging reports associated with adverse effects (17-19), underline the leading role of the principle of "safety first". Therefore, it was considered as a valuable observation that in some patients, for example in those with increased risk connected with treatment, a short-term antiarrhythmic drug therapy (4 weeks after cardioversion) can be used. It is also emphasized that the choice of the antiarrhythmic drug should be based more on the predicted safety of its use, rather than on the expected efficacy, although it is known that the probability of maintaining sinus rhythm by using the antiarrhythmic drug increases about 2 times. In a large meta-analysis of studies comparing antiarrhythmic drugs with placebo, no treatment or administration of heart rate controlling drugs, it was confirmed that drugs being both sodium antagonists with rapid (quinidine, disopyramide) and slow (propafenone, flecainide) binding kinetics, potassium channels inhibitors (dofetilide) and influencing on potassium channels and beta-adrenergic receptors (sotalol), as well as drugs affecting many ion channels with simultaneous inhibition of the sympathetic nervous system (amiodarone) significantly reduce the rate of recurrence of atrial fibrillation (20).

The choice of the antiarrhythmic drug should obviously be adapted to the patient's clinical condition. In patients without structural heart disease as the first choice of antiarrhythmic drugs dronedarone, flecainide, propafenone or sotalol are recommended (I class of recommendations, drugs given in alphabetical order), while in case of their ineffectiveness amiodarone should be given. In patients with adrenergically stimulated atrial fibrillation (an paroxysm associated with physical exertion or mental distress) or with hyperthyroidism beta-blockers should be first taken into consideration, both in order to maintain sinus rhythm and ventricular rate control in case of recurrence of AF (IIa class of recommendations). In patients with AF caused by increased vagal nerve tone, disopyramide, a drug with a significant anticholinergic impact may be considered (IIb class of recommendations). In patients with a structural cardiovascular disease (left ventricular hypertrophy, ischemic heart disease or congestive heart failure), there are established contraindications to the use of particular antiarrhythmic groups of drugs. This group of patients has acutely high risk of pro-arrhythmic and negative inotropic effects of these drugs. The risk of pro-arrhythmic effect of sotalol results from QT prolongation or from bradycardia, which may result in the occurrence of tachycardia of torsade de pointes type. Particularly at risk of pro-arrhythmic drug effect are patients with significant left ventricular hypertrophy and with heart failure. Whereas, in the study SAFE-T in patients with coronary artery disease, the benefits from the use of sotalol comparable to that of amiodarone with a relatively good safety profile was found. The QT interval should be monitored in patients treated with sotalol and if it exceeds 500 ms, the drug should be discontinued. In addition to patients with left ventricular hypertrophy, those with significant bradycardia, hypokalemia or hypomagnesemia and women are more likely to be exposed to pro-arrhythmic effect of sotalol. The last meta-analysis of studies on drugs for maintaining sinus rhythm after cardioversion indicates that the use of sotalol is associated with higher all-cause mortality compared to the control group (20-22).

In patients with atrial fibrillation with a significant cardiac disease, particularly if significant left ventricular hypertrophy and congestive heart failure occur, the only effective and safe drug drug available in Europe is amiodarone. Amiodarone directly or through its metabolite N – desethylamiodarone influences on multiple ion channels (I_{Kr}, I_{Na}, I_{Kur}, I_{to}, I_{CaL}, $I_{K,Ach}$) and activated by hyperpolarisation channel I_f. It also affects the alpha and beta-adrenergic receptors, thus demonstrating the effect of all classes of antiarrhythmic drugs. Recently, it was shown that amiodarone inhibits 2P domain of K3.1 channels, which are selectivelly expressed in the atria, prolonging the duration of the action potential in the human atrial myocytes, which may contribute to the effectiveness of amiodarone in case of AF (23). It can also be assumed that amiodarone inhibits atrial electrical remodeling process (24). There is no doubt that amiodarone is currently the most effective antiarrhythmic drug in atrial fibrillation. As it was shown in the cited SAFE-T study, amiodarone more effectively than sotalol, protected patients from recurrence of atrial fibrillation (to prevent one adverse endpoint 3 patients should be treated with amiodarone, and 8 with sotalol). In CTAF study, in which the efficacy of amiodarone in comparison to sotalol and propafenone was evaluated, it was documented that during the observation lasting 468 ± 150 days the recurrence of atrial fibrillation occurred in 63% of patients treated with sotalol or propafenone and in 35% of patients treated with amiodarone (25). In the already quoted meta-analysis of 59 clinical trials Lafuente-Lafuente the efficacy of amiodarone for prevention of recurrence of atrial fibrillation was confirmed, at the same time noting the risk of side effects including pro-arrhythmia (20). Because amiodarone inhibits many types of ion channels, the risk of torsade de pointes occurrence, despite QT interval prolongation, is lower than in the case of using pure potassium channel antagonists. Unfortunately, high amiodarone efficiency is associated with a higher occurrence (3 times when compared to other antiarrhythmic drugs) of often serious adverse effects (tab. 2).

Given the known toxic effects of long-term amiodarone using, there were serious expectations of dronedarone, an agent of analogous chemical structure, but did not containing iodine. Just like amiodarone, it is a drug influencing many sodium and potassium ion channels and affecting the antiadrenergic receptors. Initially, the results of studies made on dronedarone were very encouraging. In the DIONYSOS study less effectiveness in preventing recurrence of AF in comparison with amiodarone was demonstrat-

Table 2. Adverse effects of amiodarone (26).

Adverse effects	Incidence (%)	Symptoms	Procedure
Bradycardia	5%	bradycardia, atrioventricular block	possible need of electrostimulation
QT prolongation	most of patients	QT interspace > 500 ms	reduction in drug dose or drug withdrawal
Tachycardia of torsade de pointes type	< 1%	polymorphic ventricular tachycardia	possible need of drug withdrawal
Abnormal thyroid function	2-12%	hypothyroidism	thyroid hormones control before administering the drug, then every 3-4 months, L – thyroxine
	4-22%	hyperthyroidism	thyroid hormones control before administering on the drug, then every 3-4 months; glucocorticoids, antithyroid drugs, possible need to remove the thyroid gland
Pulmonary complications	2	cough, shortness of breath, inflammations, fibrosis in imaging studies	often the drug withdrawal, glucocorticoids
Liver function disorders	15%	ALAT, AST > 2 x exceeds the norm, inflammation or cirrhosis	consideration of drug withdrawal, liver biopsy
Eye complications	> 90%	presence of deposites in the cornea	the presence of deposits in the cornea is not an indication for drug withdrawal
	< 1%	optic neuropathy	ophthalmological consultation, drug withdrawal
	< 5%	symptoms of 'halo' (seeing objects with the color coating, mainly at night)	ophthalmological consultation
Skin complications	< 10%	change of colour (blue-gray)	reduce the dose of the drug
	25-75%	sensitivity to light	reduction in drug dose, avoiding of sunlight, UV filters, dermatological consultation
Inflammation of testicles or epididymis	1% of men	pain	urology consultation
Neurological complications		ataxia, paresthesia, peripheral neuropathy, sleep disorders	reduction in drug dose, neurological consultation if neccessary

ed (55 vs 74%, $p < 0.001$), but the drug was reported as safe – had no effect on thyroid function, showed less, than amiodarone, adverse effects on digestive system. There was also observed no significant interactions with warfarin (27). In subsequent studies on the efficacy and safety of dronedarone there was reported a reduced amount of hospitalizations caused by cardiovascular reasons and decreased mortality (ATHENA), effectiveness in preventing the recurrence of AF (EURIDIS and ADONIS), high efficacy in reducing ventricular rate (ERATO). All cited studies emphasized favolable drug safety profile (28-31). After the observed, in ATHENA study a decreased incidence of cardiovascular events, in a small subpopulation of patients with permanent atrial fibrillation, there was performed PALLAS study to compare the effects of dronedarone to placebo, both administered simultanously with previously selected optimal pharmacotherapy, in patients with permanent AF (lasting not less than 6 months) and with serious cardiovascular disease. The study was prematurely discontinued due to a significant increase in the number of cardiovascular events including increased mortality in the group treated with dronedarone. As a result, according to the current ESC guidelines dronedarone is not recommended in patients with permanent AF, especially in patients with significant cardiovascular diseases, who constituted a large part of the group treated with dronedarone in PALLAS study (32). On the basis of ANDROMEDA study, it was found that the administration of dronedarone in patients with heart failure from III or IV NYHA class worsens the prognosis (increases mortality in the dronedarone group in patients with heart failure and EF < 35%) (33). However, there are doubts about the safety of the drug in patients with less severe heart failure (functional classes NYHA I and II), although in the PALLAS study, there was no relationship between the severity of heart failure and the occurrence of any unfavourable outcomes. In none of the studies any proarrhythmic effect of dronedarone was observed and after the approval of the drug in clinical practice only a few cases of torsade de pointes were reported, and therefore it appears that the treatment with dronedarone can be used in patients with hypertension and left ventricular hypertrophy. On the other hand, the drug should not be combined with digoxin (increased incidence of sudden death in the PALLAS study) and it should be avoided with dabigatran, as dronedarone as an P-glycoprotein inhibitor may increase concentration of dabigatran in serum and result in bleeding complications.

Given the emerging, in recently publised data, evidence of adverse effects associated with dronedarone use, the current recommendations for the use of the drug are limited to maintain sinus rhythm in patients with recurrent AF without a significant structural heart disease. Dronedarone can be used to maintain sinus rhythm after cardioversion, but if it is decided to sustain AF in a patient, treatment should be discontinued. The drug is not advisable for patients with moderate or severe heart failure. It must also be avoided in patients with less advanced heart failure (I and II NYHA class), unless there is no suitable alternative. The initiation of treatment should take place in controlled conditions, during hospitalization or in a clinic under the supervision of a specialist experienced in antiarrhytmic agents treatment.

DRUGS USED TO CONTROL VENTRICULAR RATE

In guidelines for atrial fibrillation, among drugs for control of ventricular rate there were beta-blockers, non-dihydropyridine blockers of calcium channels, digoxin (IB class of recommendations) and amiodarone, although the latter, because of its side effects, received a low recommendation of IIb class. Also dronedarone can be used (IIa class of recommendations), but due to the results of the already quoted PALLAS study it can be used exclusively in patients with non-permanent atrial fibrillation and without symptoms of heart failure.

Beta-blockers, non-dihydropyridine blockers of calcium channels and digoxin, are drugs which can be used to control ventricular rate in patients with paroxysmal, persistent or permanent atrial fibrillation, and the choice of the drug should depend on the patient's clinical characteristics. Beta-blockers are characterized by being particularly effective in the case of adrenergic system stimulation, and in patients with coronary heart disease. Non-dihydropyridine calcium antagonists are drugs with similar efficacy and safety to beta-blockers. However, they should not be used in patients with systolic heart failure due to the known inotropic – negative effect. In patients with heart failure, impaired left ventricular function or in those leading a sedentary lifestyle the use of digoxin should be considered (IIa class of recommendations). However, digoxin should not be administered as the only drug to control ventricular rate in patients with paroxysmal atrial fibrillation. In patients resistant to other drugs an amiodarone may be effective. It is well tolerated by patients hemodynamically unstable and can be given directly to control ventricular rate. Amiodarone can also be long-term used but in patients previously treated with amiodarone for rhythm control, after the decision to sustain atrial fibrillation, change of drug to other safer agents should be considered. According to experts, other antiarrhythmic drugs for the control of ventricular rate in patients with permanent atrial fibrillation should not be used. In patients treated with sotalol in order to maintain sinus rhythm an additional effect of rate control can be observed, but the drug should not be used solely for that purpose. A unique group consists of patients with pre-excitation syndrome, in whom during paroxysmal atrial fibrillation or in the case of atrial fibrillation in medical history, in order to control ventricular rate, a propafenone or amiodarone are preferred, because of prolonging the conduction also in an additional pathway (IC class of recommendations). However, it should not be forgotten that in this group of patients the RF ablation of an additional pathway received a IA class of recommendations.

UPSTREAM THERAPY

Among the drugs that are not strictly antiarrhythmic agents, taking a part of a strategy to prevent the occurrence of atrial fibrillation ACE inhibitors and angiotensin receptor blockers, and also spironolactone, statins, and unsaturated fatty acids should be mentioned. None of the recently published controlled studies reffering to the use of angiotensin receptor blockers did not confirm the effectiveness of treatment to prevent recurrence of AF. Similar results were obtained by most of the studies comparing polyunsaturated fatty acids with placebo (34, 35). However, a combined use of drugs that affect the RAA system with antiarrhythmic drugs in order to increase the likelihood of maintaining sinus rhythm can be justified (36, 37).

NEW ANTIARRHYTHMIC DRUGS

Many antiarrhythmic drugs used in atrial fibrillation influencing the ion channels not only causes prolongation of the atrial refractory period, but also by QT interval prolongation exerts a proarrhythmic effect. Hence, agents with selective impact (or with dominant effect) on ion channels in the atria are currently trying to be found. Among the ion channels, which are potential targets of drugs selectively acting in atrial I_{Kur} and $I_{K,Ach}$ channels are mentioned. As it was shown in animal studies, a relatively selective inhibitor of I_{Kur} channel, KVI-0201, reduces the rate of atrial fibrillation triggering. Other agent XEN-D0103, characterizing by a high selectivity with respect to I_{Kur} channel prevents the occurrence of atrial fibrillation in dogs triggered by fast stimulation, and now it undergoes clinical studies of I phase (38). Because in atrial fibrillation the enhanced inwards potassium current stabilizes the rotors and increases re-entry phenomenon it seems that blocking of $I_{K,ACh}$ channel may occur to be antiarrhythmic strategy selective for atria. Among the agents selectively blocking this ion channel the most advanced research concern the NTC-801, which is in phase II of clinical studies. As the studies on animals showed, the agent prevents the triggering of atrial fibrillation by rapid atrial stimulation and by stimulation of the vagal nerve in dogs. Because of the expression of $I_{K,ACh}$ channels also in the Purkinje fibers and in cells of the sinus node and atrioventricular node, the drug may cause tachycardia and it can enhance atrioventricular conduction or automaticity of Purkinje cells, and also may affect nervous system, as it penetrates the blood-brain barrier. However, so far ventricular pro-arrhythmic effects have not been reported (39).

There are studies, still ongoing, that aim at evaluating the antiarrhythmic effect of ranolazine – that inhibits the late sodium current. In a MERLIN-TIMI36 clinical study except of the preventing stenocardia in the group of patients treated with ranolazine, a significant reduction in the incidence of arrhythmias, including AF was observed. Antiarrhythmic effect of ranolazine is primarily due to the inhibition of the late sodium current, but the drug also inhibits I_{Kr}, I_{Ks} currents and possibly $I_{Ca,L}$ (40-42). In the RAFAELLO study the efficacy of three different doses (375, 500 and 750 mg) of ranolazine in maintaining sinus rhythm following electrical cardioversion of atrial fibrillation was compared with placebo (43). There was no evidence that any dose significantly prolonged the time to recurrence of AF, but the number of arrhyrhmia returns in patients treated with higher doses of ranolazine was smaller. In the HARMONY study combined therapy with ranolazine or dronedarone and with amiodarone was assesed. Among the five groups of patients examined in this study the most beneficial were patients treated with ranolazine, at a dose of 2 x 750 mg

and with dronedarone (in 45% of patients the reduction of arrhythmia was achieved by > 70%).

Blocking of calcium-dependent SK channels seems to be the another promising strategy. Experimental studies demonstrated that the NS8593 and UCL1684 agents prevent the occurrence of AF triggered by stimulation in guinea pigs and rats. It was also found that blocking SK channel using apamine has no significant effect on the total ion efflux across a cell membrane of atrial myocytes in the case of sinus rhythm, and significantly reduces the total ion membrane flow in the case of atrial fibrillation (44, 45). A new approach to prevent the re-entry phenomenon maintaining atrial fibrillation may be the restoration of the uniform conduction by modulating cellular connections (gap junction). Although, the first agent, enhancing the phosphorylation of connexin-43 dependent on PKC (rotigaptid) was withdrawn from clinical studies, new modulators of cellular connections, for example danagaptid are synthesized. There are also performed experimental studies in order to determine the usefulness of gene therapy using adenoviruses transferring connexin genes 40 and 43, which enables the proper expression of connexins and restores normal intercellular conduction (46).

Other new antiarrhythmic drugs act by of inhibiting the remodeling of the atria. More and more experimental studies confirm the important role of electrical remodeling dependent from cellular signals, which largely depends on the proper flow of calcium through ion channels of cardiomyocytes. Electrical remodeling of $I_{Ca,L}$ channel via activation of the NFAT pathway could be prevented by the inhibition of calcium dependent phosphatase of calcineurin (47). Also other kinases and protein phosphatases and their regulators may be potential targets for new antiarrhythmic drugs. For example, inhibition of calpain, calcium-dependent proteolytic enzyme, normalizes the creatine phosphokinase dependent (PKC) regulation of the $I_{K,ACh}$ channel (48). Calcium/calmodulin dependent kinase II also plays a significant role. Kinases bind ryanodine receptor (RYR2), phospholamban, and also calcium channels L and sodium channels. An increased phosphorylation of RyR2 in the case of atrial fibrillation may result from local loss of activity of the protein phosphatase 1 (PP1), due to increased activity of inhibitor PP-1 in sarcoplasmic reticulum (SR). Reduced PP1 activity may also contribute to excessive PLN phosphorylation and hyper phosphorylation of RyR2 receptor, which causes calcium overload and an increased calcium leakage from the SR. In contrast, the increased phosphatase activity may decrease the activity of the $I_{Ca,L}$ channel in atrial fibrillation (49, 50).

In addition to potential inhibition of atrial electrical remodeling, scientists are looking for a substance that may inhibit structural remodeling. A pirfenidone, drug that inhibits lung fibrosis, preventing, as it was demonstrated in animal model studies, atrial fibrillation in dogs with heart failure was evaluated as a first drug of this group. Pirfenidone inhibits the pathway of TGF-β1 and TNF-α pathways and the nitric oxide synthase. However, due to the activation of the $I_{Ca,L}$ channel and the prolongation of APD, which may contribute to ventricular pro-arrhythmia, no further clinical studies were taken on the use of this drug in case of AF. Among other substances that inhibit cell signaling pathways an inhibitors of increased expression of TRPM7 and/or TRPC3 channels are mentioned. First of these pathways is also inhibited by the already mentioned NS8593 and UCL1684 substances, inhibiting SK channels (51).

Recently, there are also conducted genetic studies on the regulation of both electrical and structural atrial remodeling by microRNA molecules (miR). In experimental reaserches it was shown that the inhibition of miR activity through the use of complementary nucleotide sequences (antagomirs) may contribute to the inhibition of myocyte fibrosis (52).

CONCLUSIONS

Despite many years of experience, antiarrhythmic treatment of atrial fibrillation still remains a difficult problem. Deciding on the administration of antiarrhythmic drug after exhausting all treatment options, both causal and upstream therapy, not only effectiveness has to be taken into account, but first at all the safety of the treatment. We are still far from receiving a perfect antiarrhythmic drug, working selectively on atrial cells, safe in patients with heart disease, characterizing by a low risk of side effects or damage to internal organs, with a long half-life period allowing for dosing once a day and without interactions with other drugs. Using currently available agents we should initiate treatment with a beta-blocker, that frequently is not very effective, but usually rather safe. Next, a typical antiarrhythmic drug can be chosen following the current guidelines and the own clinical experience and availability of particular agent. It can be hoped that as the science develops, in clinical practice there will appear antiarrhythmic drugs, that will allow most patients to safely maintain the physiological sinus rhythm.

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received/otrzymano: 08.06.2015
accepted/zaakceptowano: 09.07.2015