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SHORT COMMUNICATION

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Electrophysiological Effects of a New Antiarrhythmic Drug Aksaritmin

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Abstract

The purpose of this report was to study the pharmacodynamics of aksaritmin and its effect on cardiac electrophysiological parameters in patients with various heart arrhythmias.

Materials and Methods: Fifty-one patients with various heart arrhythmias aged between 18 and 60 years (mean age of 38.4±11.6 years) were examined. The effect of aksaritmin on cardiac electrophysiological parameters was studied using 12 lead ECG, transesophageal electrophysiological study (TES) and intracardiac electrophysiological study (EPS). Effects of aksaritmin (25-50 mg per os) were studied in an acute drug test (ADT) (3 hours after the start of testing) and during the course of treatment (on the fifth day). TES was performed on patients with paroxysmal tachycardias. Aksaritmin was used once at a dose of 50 mg per os, and all indicators were measured 3 hours after patients took the drug. In TES, we studied the sinus-node recovery time (SRT), the Wenckebach point, ERP of the atrioventricular node (ERP-AVN) and accessory atrioventricular connection (ERP-AAVC). The effect of the drug in intracardiac EPS was studied 3 hours after patients were given a single dose of aksaritmin (50 mg) per os. All parameters were measured according to the standard EP protocol.

Results: The action of aksaritmin begins 45-60 minutes after the drug is taken and reaches a maximum after 3-4 hours; effects last an average of 8 hours, which allows one to prescribe aksaritmin 3 times a day. The drug in ADT and during the course of treatment increases HR by 8.1% and 4.9%, respectively. Aksaritmin slows down the conduction of impulses via the atria, AV node and His-Purkinje system, and does not affect ventricular ERP. Accordingly, on ECG, the duration of PQ interval and QRS complex is significantly longer, while the duration of the QTc interval does not change. Aksaritmin prolongs ERP-AVN in the retrograde direction by 8.1% and completely blocks anterograde conduction via the AAV pathway in WPW patients. (**International Journal of Biomedicine. 2019;9(2):179-181.**)

Key Words: aksaritmin • pharmacodynamics • electrophysiological parameters • effective refractory period

Abbreviations

AAD, antiarrhythmic drugs; **AAE**, antiarrhythmic effect; **ADT**, acute drug test; **ERP**, effective refractory period; **EPP**, electrophysiological parameters; **EPS**, electrophysiological study; **HR**, heart rate; **PVCs**, premature ventricular contractions; **PSVCs**, premature supraventricular contractions; **SE**, side effects; **TES,** transesophageal electrophysiological study; **WPW**, Wolff-Parkinson-White syndrome; **WP**, Wenckebach point.

Introduction

As is known, the algorithm for prescribing AAD is primarily based on the safety of the drug in a particular heart disease, and then the effectiveness of the drug in a given heart arrhythmia.[1] Unfortunately, any AAD has side effects that also reduce the patient's quality of life. In this regard, it seems relevant to create new AAD, which not only eliminate the arrhythmia itself, but also have minimal SE. One of the drugs [2,3] successfully used in patients with heart arrhythmias, without or with minimal organic heart disease, is allapinin. However, many studies have identified dose-dependent central nervous system side effects (dizziness, pressure in the head, diplopia) of allapinin (from 18% to 65%), which limit its scope and require discontinuation of the drug in up to 10% of cases.[4]

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The researchers at the Institute of the Chemistry of Plant Substances (ICPS) of the Academy of Sciences of the Republic of Uzbekistan have created a new AAD—aksaritmin. Aksaritmin, as well as allapinin, is obtained from the roots of Aconitum septentrionale. The technology of its production is simpler, and the economic cost is 1.5-2 times lower than that of allapinin. On the basis of IASD, experimental studies on various laboratory animals were conducted, which showed high efficacy and safety of the drug in reproducible ventricular and supraventricular arrhythmias.[5,6] The Republican Specialized Center of Cardiology continues to study the clinical and electrophysiological properties of aksaritmin in patients with various heart arrhythmias. The purpose of this report was to study the pharmacodynamics of aksaritmin and its effect on cardiac EPP in patients with various heart arrhythmias.

Materials and Methods

Fifty-one patients with various heart arrhythmias aged between 18 and 60 years (mean age of 38.4±11.6 years) were examined. Of 8 patients with WPW syndrome, 4 were diagnosed with a manifest form, 2 had an intermittent form, and 2 patients had a latent form of WPW syndrome, which was diagnosed during TES. An intracardiac EPS was performed on 10 patients. Inclusion criteria were frequent PVCs and/or PSVCs, including high gradations, frequent paroxysmal supraventricular tachycardia in patients with the absence or minimal manifestations of organic heart disease. The exclusion criteria were age of patients <18 years and >60 years, acute myocardial infarction (MI), MI history, unstable angina, NYHA III-IV with LVEF<50%, wall thickness <14mm, sick sinus syndrome, second- or third-degree AV block, hepatic and renal failure and other comorbidities in the decompensated stage, pregnancy and lactation, taking other AAD.

The study protocol was reviewed and approved by the Ethics Committee of the Republican Specialized Centre of Cardiology. All participants provided the written informed consent.

The effect of aksaritmin on cardiac EPP was studied using 12 lead ECG, TES and intracardiac EPS (n=10).

Effects of aksaritmin (25-50 mg per os) using 12 lead ECG were studied in an ADT (3 hours after the start of testing) and during the course of treatment (on the fifth day).

TES was performed on patients with paroxysmal tachycardias. Aksaritmin was used once at a dose of 50 mg per os, and all indicators were measured 3 hours after patients took the drug. In TES, we studied the sinus-node recovery time (SRT), WP, the ERP of the atrioventricular node (ERP-AVN), and the ERP of accessory atrioventricular connection (ERP-AAVC).

The effect of the drug in intracardiac EPS was studied 3 hours after patients were given a single dose of aksaritmin (50 mg) per os. All parameters were measured according to the standard EP protocol with assessment by such indicators as P-wave duration, RR, PQ, QRS, QT, QTc, PA, AH, HV, spike H duration, anterograde and retrograde WP (AWB/RWB), anterograde and retrograde ERPs of the atrioventricular node (AERP-AVN/RERP-AVN), ERP of the right ventricle (ERP-RV), and the right and left atrial ERPs (ERP-RA, ERP-LA).

The statistical analysis was performed using the statistical software «Statistica» (v6.0, StatSoft, USA).

Results and Discussion

The pharmacodynamics of aksaritmin was studied in 51 patients of both sexes with consistently frequent PVCs or PSVCs. Of the 8 patients taking aksaritmin at a dose of 12.5 mg, only one patient experienced a positive AAE with suppression of PVCs by more than 90%. At the same time, AAE of aksaritmin began after 60 minutes and lasted up to 8 hours.

When prescribing aksaritmin at a dose of 25 mg, 10(43.5%) of the 23 patients achieved AAE, which consisted in a decrease in the number of PVCs/PSVCs by an average of 80% for more than 8 hours, while in 5(21.7%) patients there was complete suppression of PVCs/PSVCs. When prescribing aksaritmin at a dose of 50 mg, positive AAE was observed in 15(75%) of 20 patients, with complete suppression of arrhythmias observed in 5(25%) patients. In another 10(50%) patients, the number of PVCs/PSVCs decreased by more than 70%, but in one patient, the effect was short-lived (5 hours).

In general, AAE of aksaritmin lasted from 5 to 12 hours (average of 8.1±1.2 h), which allows us to conclude that the drug can be administered 3 times a day and in some patients, 4 times a day.

ECG data

In ADT and course of treatment, aksaritmin increased HR by 8.1% (P<0.05) and 4.9% (P>0.05), respectively. Aksaritmin in ADT significantly increased the PQ interval by 9.4% (P<0.05), while during the course of treatment, this indicator increased slightly less—by 7.3% (P<0.05). The width of the QRS complex significantly increased by 10.8% (P<0.05) in ADT and by 7.8% (P<0.05) on the fifth day of the course of treatment. Changes in the QTc interval while patients were taking the drug were statistically insignificant.

TES data

EPP were studied in patients with WPW syndrome with atrioventricular reciprocating tachycardia (AVRT) and orthodromic atrioventricular reciprocating tachycardia (OAVRT). Studies were conducted before and 5 days after drug taking. In this report, we present only the effect of the drug on the heart ERP.

We found that aksaritmin shortened the duration of the cardiac cycle from 747 msec to 693 msec (7.2%). In patients with normal sinus-node function, aksaritmin reliably shortened the duration of the cardiac cycle, and at the same time, it practically did not change SRT. Aksaritmin did not affect such an indicator as WP, while it insignificantly shortened ERP-AAVC by 5% (from 321±44 msec to 305±42 msec). In patients with a latent form of WPW syndrome with OAVRT (n=2) and typical AVRT (n=11), in the absence of a significant effect on anterograde AV conduction, the drug prevented paroxysm induction in 7 patients with AVRT, which indicates blocking of the retrograde knee of the re-entry circle (conduction via the accessory pathway or via the fast AV nodal pathway).

In patients with induced tachycardia with repeated TES, the drug lengthened the VA interval by 9.4% and AV by 10.4%, both in AVRT and orthodromic tachycardia, which indicates that the impulse is slowed down as retrograde (the fast AV nodal pathway and accessory pathway) and antegrade (via AV connection). Due to the slowing down of the impulse in inducing persistent paroxysmal tachycardia, the A-A interval was significantly longer, by 6.6%, which indicated a decrease in the frequency of tachycardia, despite the fact that the drug was not effective in preventing a recurrence of tachycardia.

It should be noted that in two patients with an intermittent form of WPW syndrome on the daily ESG monitoring and frequent atrial stimulation, there were no signs of pre-excitation, i.e. aksaritmin also completely blocked anterograde conduction via the AAV pathway.

Intracardiac EPS data

It was established that aksaritmin in a dose of 50 mg slowed down the rate of impulses in various parts of the cardiac conduction system. The speed of the pulses in the atria (RA interval) slowed down from 22.9 msec to 27.7 msec (P <0.05). The AV nodal conduction time (AH interval) was also lengthened reliably by 8.2%. The His-Purkinje system conduction time slowed down significantly by 21.8%. As a result, the PQ interval was prolonged from 144 msec to 160.5 msec (P<0.05) and the QRS duration from 80.7 msec to 87.4 msec (P<0.05).

The duration of ERP-AVN was insignificantly reduced in the anterograde direction, while in the retrograde direction ERP-AVN was prolonged by 8.1% (P<0.05). The drug significantly reduced the duration of the refractory period of the His-Purkinje system, but practically did not change ERP-RV. On the ECG, respectively, the duration of the QTc interval was practically unchanged.

The effect of aksaritmin on atrial ERP in the studied patients was non-unidirectional. Thus, ERP-RA increased in 2 patients, shortened in one patient, and in 7 patients remained unchanged.

ERP-LA was shortened in 5 patients, lengthened in 3 patients and did not change in 2 patients. At the same time, the average indices of atrial ERP were not statistically significantly changed.

It should be emphasized that in our study, we measured the ERP-RA only in the upper section, which may explain the results obtained by the different directions of the drug's action. It should also be noted that the drug was studied in a small amount—only in 10 patients—which also plays an important role in the statistical evaluation of research results.

On the whole, according to 12 lead ECG and EPS data, the effects of aksaritmin coincide with the effects of AAD class IC (the Vaughan Williams classification). They are characterized by a pronounced negative effect on the rate of impulses in the atrial and ventricular myocardium, as well as in the specialized intraventricular conduction system of the heart. At the same time, the duration of refractory periods varies slightly.

Conclusions:

- The action of aksaritmin begins 45-60 minutes after the drug is taken and reaches a maximum after 3-4 hours; effects last an average of 8 hours, which allows one to prescribe aksaritmin 3 times a day.
- Aksaritmin in ADT and during the course of treatment increases HR by 8.1% and 4.9%, respectively.
- Aksaritmin slows down the conduction of impulses via the atria, AV node and His-Purkinje system, and does not affect ventricular ERP. Accordingly, on ECG, the duration of PQ interval and QRS complex is significantly longer, while the duration of the QTc interval does not change.
- Aksaritmin prolongs ERP-AVN in the retrograde direction by 8.1% and completely blocks anterograde conduction via the AAV pathway in WPW patients.

Competing Interests

The authors declare that they have no competing interests.

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