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Comparative Effectiveness of Aksaritmin and Propafenone in the Prevention of Atrial Fibrillation

Husniddin Sh. Kuchkarov*, Nodir U. Zakirov, Ravshanbek D. Kurbanov

Republican Specialized Center of Cardiology, Tashkent, Uzbekistan

Abstract

Background: The purpose of this study was to evaluate the efficacy of Aksaritmin (Aks) in comparison with Propafenone (Pr) for the prevention of atrial fibrillation (AF) in patients with none or minimal signs of structural heart disease.

Methods and Results: The study included 60 patients aged 18-70 years (mean age of 58.1±7.7 years) with paroxysmal (frequency of more than 2 paroxysms/3 months episodes of AF) or persistent AF with no or minimal signs of structural heart disease. The patients were divided into two groups: Group 1 included 30 patients taking Aks, and Group 2 included 30 patients taking Pr. According to the study protocol, the starting dose of Aks was 75 mg/day, with a possible dose increasing to 112.5 mg/day. The starting dose of Pr was 450 mg/day, with a possible dose increase to 600 mg/day.

In Group 1, preventive efficacy of Aks was observed in 29(96.7%), 26(86.7%), and 24(80%) patients by 1-, 3- and 6-month follow-up, respectively. Of these, 26(86.7%), 22(73.9%), and 16(53.3%) patients showed absolute preventive efficacy of the drug. In Group 2, preventive efficacy of Pr was observed in 28(93.3%), 26(86.7%), and 23(76,7%) patients at 1-, 3- and 6-month follow-up, respectively. Of these, 25(83.3%), 21(70%), and 14(46.7%) patients showed absolute AAE of the Pr.

The initial recurrence rate of AF was 4.5±1.4 and 4.2±1.3 in Groups 1 and 2, respectively (P=0.3933 between groups); but after 3 and 6 months of therapy, the recurrence rate decreased to 0.7±1.1 (P<0.0001) and 0.8±1.3 (P<0.0001), and 0.8±1.0 (P<0.0001) and 1.1±1.0 (P<0.0001), respectively, which was statistically significant in both groups.

Conclusion: The preventive efficacy of Aks (including in combination with BB) at a dose of 75-112.5 mg/day in recurrent forms of AF is comparable to the "reference" drug Pr at a dose of 450-600 mg/day.**(International Journal of Biomedicine. 2023;13(2):224-228.)**

Keywords: atrial fibrillation • antiarrhythmic efficacy • propafenone • aksaritmin

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Abbreviations

AAE, antiarrhythmic efficacy; **AF,** atrial fibrillation; **AADs**, antiarrhythmic drugs; **AAE**, antiarrhythmic efficacy; **ACEI**, angiotensin-converting enzyme inhibitors; **ARB**, angiotensin II receptor blockers; **BB**, beta-blockers; **CCB**, calcium channel blockers; **LA**, left atrial; **LVEF,** left ventricular ejection fraction.

Introduction

Atrial fibrillation (AF) is one of the most common forms of heart rhythm disturbances with substantial medical and social significance. The current prevalence of AF in adults is between 2% and 4%. It is expected to increase 2.3-fold due to increased life expectancy in the general population and an increased search for undiagnosed AF.

Propafenone (Pr) is a Class Ic antiarrhythmic agent, which is highly efficient in restoring sinus rhythm in patients with paroxysms of AF and is a reasonably fast action. A series of controlled trials in patients with recent-onset AF without heart failure who were hospitalized with enforced bed rest has shown that orally taken propafenone (450 to 600 mg as a single dose) exerts a relatively quick effect (within 3 to 4 hours) and a high rate of efficacy (72% to 78% within 8 hours). At the

***Corresponding author**: Husniddin Sh. Kuchkarov, Ph.D. Republican Specialized Center of Cardiology. Tashkent, Uzbekistan. E-mail: hus_doc@mail.ru*

same time, Pr is a highly effective "rhythm control" drug in AF. In a recent update of the 2006, 2012, and 2015 reviews (the mean follow-up period was 10.2 months), moderate- to high-certainty evidence showed that propafenone reduced the recurrence of AF (RR=0.67, 95% CI: 0.61 to 0.74).

In Uzbekistan, besides Pr, AF is treated with such antiarrhythmic drugs (AADs) as ethacizine hydrochloride (ethacyzine), lappaconitine hydrobromide (allapinin), and amiodarone. Flecainide is not registered. Among these drugs, allapinin is distinguished by its plant origin. After *per os* administration of allapinin in patients with AF, the frequency of atrial impulses naturally decreases up to transformation into atrial flutter (in 14% of cases), after which, in 71% of cases, sinus rhythm is restored.

Allapinin was included in National and Eurasian guidelines for preventing AF and restoring sinus rhythm. However, in some cases (18%–65%), there are side effects on the central nervous system (dizziness, headache, diplopia), which have limited the scope of its administration and have resulted in patients refusing to take the drug in up to 10% of cases. In this regard, because of scientific and practical interest, a new AAD – aksaritmin (Aks) – was developed at the Yunusov Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan. It contains nine alkaloids, similar in chemical structure to allapinin. Aks is obtained from the roots and rhizomes of the *Aconitum septentrionale*. The technology for its production is much simpler than that for allapinin, and the economic cost of obtaining raw materials is two times lower.

It is recognized that the composition of allapinin mainly contains lappaconitine (up to 80%). The content of N-Deacetyllappaconitine monochlorhydrate—the main metabolite of lappaconitine hydrobromide, which is not inferior to lappaconitine hydrobromide in activity, but is less toxic—in the composition of allapinin does not exceed 5%. In contrast to allapinin, in the composition of Aks the proportion of lappaconitine hydrobromide is less, about 40%-60%, while N-Deacetyllappaconitine monochlorhydrate is greater, about 10%-20%. According to the developers, due to this ratio of components, in various experimental models of cardiac arrhythmias, Aks showed less toxicity and greater therapeutic latitude.

The purpose of this study was to evaluate the efficacy of Aks in comparison with Pr for the prevention of AF in patients with none or minimal signs of structural heart disease.

Materials and Methods

The study included 60 patients aged 18-70 years (mean age of 58.1±7.7 years) with paroxysmal (frequency of more than 2 paroxysms/3 months episodes of AF) or persistent AF with no or minimal signs of structural heart disease. Exclusion criteria were valvular heart disease, acute coronary syndrome, chronic heart failure (NYHA FC I-IV), sinus node dysfunction, second-third-degree AV block, LV wall hypertrophy over 14 mm, taking other AADs within the last 5 days (2-4 weeks if taking amiodarone), pregnancy and lactation, thyroid diseases, and other conditions with the need to correct the hormonal status.

The patients were divided into two groups: Group 1 included 30 patients taking Aks, and Group 2 included 30 patients taking Pr. Patients in both groups were comparable in baseline characteristics (Table 1). According to the study protocol, the starting dose of Aks was 75 mg/day (one pill every 8 hours), with a possible dose increasing to 112.5 mg/day. The starting dose of Pr was 450 mg/day, with a possible dose increase to 600 mg/day. Using 24-hour Holter ECG monitoring (HMECG), the AAE of drugs was assessed on Days 4-5 (for safety assessment) of the start of therapy as well as at the stages of 1, 3, and 6 months of follow-up against the background of standard therapy for the underlying disease. According to the study protocol the AAE of the drugs was recorded with a decrease in the number of paroxysms by 70% or more (moderate-high positive AAE) from the initial level and with the elimination of episodes of AF by 100% (absolutely positive AAE).

Table 1.

Baseline characteristics of study patients.

Variable	Group 1 (n=30)	Group 2 (n=30)
Age, years	57.±7.9	58.7±8.5
Male, n (%)	17 (56.7)	19 (63.3)
Paroxysmal AF, n (%)	26 (86.7)	25 (83.3)
History of AF, months	16.3±3.4	15.2±3.8
CHA2DS2-VASc, score	1.8	1.9
LA, mm	36.5±4.8	35.8±4.5
LVEF, %	62.8±3.5	63.1±4.1
Mitral regurgitation Grade I, n (%) Grade II, n (%) Grade III-IV, n (%)	 14 (46.7) 0 0	 13 (43.3) 0 0
Medication Anticoagulants, n (%) ACEI/ARB, n (%) Beta-blockers, n (%) CCB, n (%)	 25 (83.3) 24 (80) 19 (63.3) 2 (6.7)	 24 (80) 25 (83.3) 12 (40) 3 (10)

All patients at the beginning of the study underwent electrocardiography (ECG), including an acute drug test, echocardiography (Echo), HMECG, ultrasound of the liver, kidneys, and thyroid gland, and a biochemical blood test to exclude concomitant conditions potentially generating AF. Given that Aks belongs conditionally to the Class Ic of AADs, special attention was paid to Echo parameters. In addition to Aks and Pr, patients were prescribed standard therapy in accordance with the underlying disease.

Statistical analysis was performed using the statistical software «Statistica» (v13.0, StatSoft, USA). Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean±standard deviation (SD) for continuous variables. Inter-group comparisons were performed using Student's t-test. Group comparisons with respect to categorical variables were performed using the chi-square test. A probability value of $P<0.05$ was considered statistically significant.

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

Results

The main disease was essential hypertension, observed in 24(80%) patients in Group 1 and 22(73.3%) patients in Group 2. Six (20%) patients in Group 1 and 8 (26.7%) patients in Group 2 suffered from chronic persistent myocarditis.

In Group 1, preventive efficacy of Aks was observed in 29(96.7%), 26(86.7%), and 24(80%) patients by 1-, 3- and 6-month follow-up, respectively. Of these, 26(86.7%), 22(73.9%), and 16(53.3%) patients showed absolute preventive efficacy of the drug (Figure 1).

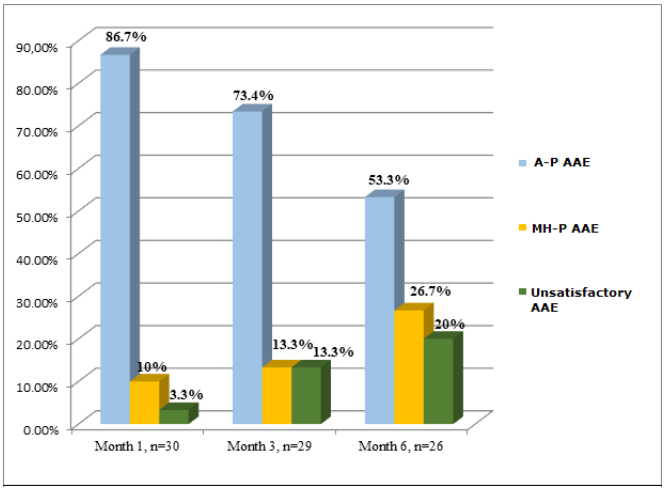

Fig. 1. *Preventive efficacy of aksaritmin in AF.*

In Group 2, preventive efficacy of Pr was observed in 28(93.3%), 26(86.7%), and 23(76,7%) patients at 1-, 3- and 6-month follow-up, respectively. Of these, 25(83.3%), 21(70%), and 14(46.7%) patients showed absolute AAE of the Pr (Figure 2).

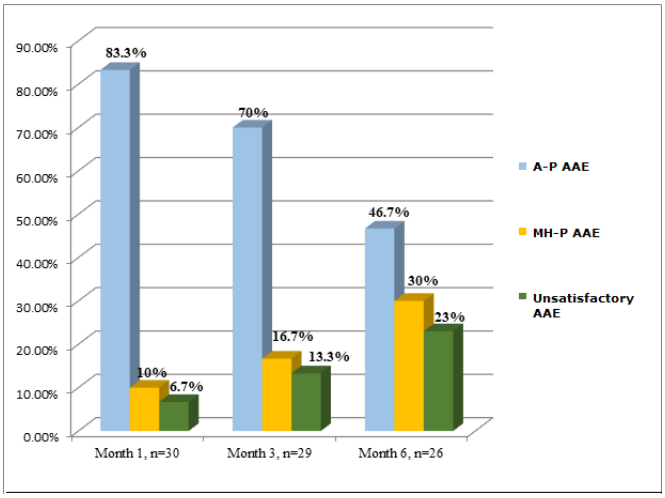

Fig. 2. *Preventive efficacy of propafenone in AF.*

In patients with an unsatisfactory AAE of the drugs, the dose of Aks was increased to 112.5 mg/day and Pr to 600 mg/day.

The initial recurrence rate of AF was 4.5±1.4 and 4.2±1.3 in Groups 1 and 2, respectively (P=0.3933 between groups); but after 3 and 6 months of therapy, the recurrence rate decreased to 0.7±1.1 (P<0.0001) and 0.8±1.3 (P<0.0001), and 0.8±1.0 (P<0.0001) and 1.1±1.0 (P<0.0001), respectively, which was statistically significant in both groups (Figure 3).

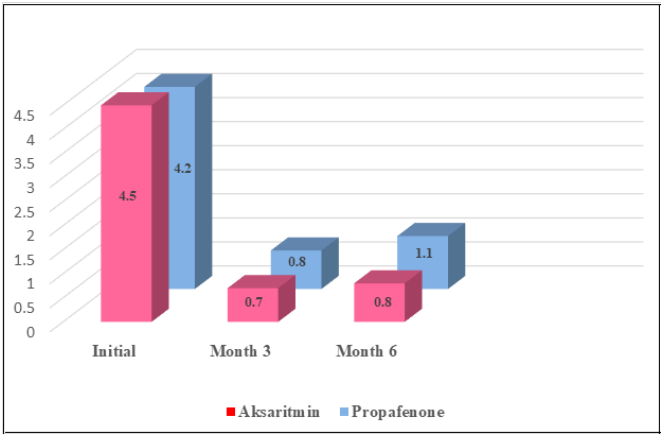

Fig. 3. *Dynamics of the frequency of AF recurrence during treatment.*

Aks and Pr were used either as a single AAD to prevent AF recurrence or in combination with beta-blockers (BB). The combination with BB in the Aks group was observed in 63.3% of cases, and in the Pr group in 40% of cases. A greater percentage of the combination of Aks with BB, compared to Pr, is explained by the fact that with Aks, the heart rate tends to increase, and with Pr it slows down (due to the presence of beta-blocking properties in Pr). Given this circumstance, in our opinion, it was advisable to evaluate the AAE of Aks without and in combination with BB. Aks in combination with BB had AAE in 100% and without BB in 90.9% of cases after one month of therapy ($\chi 2$=1.729; P=0.1885). After 3 and 6 months of therapy, AAE of Aks with BB and without BB was found in 89.5% and 81.8% ($\chi 2$=0.346; P=0.5565), and 84.2% and 72.7%, respectively ($\chi 2$=0.556; P=0.4558) (Figure 4).

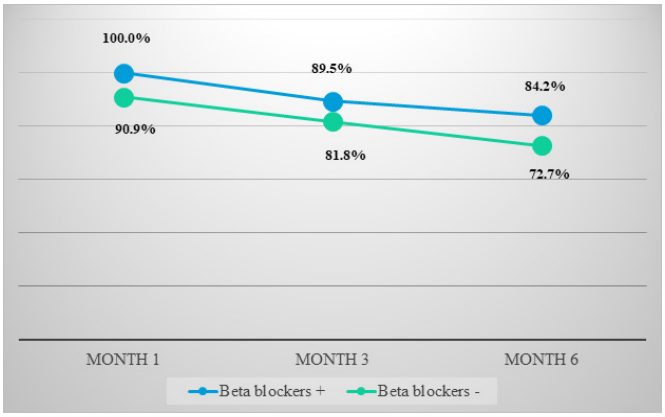

Fig. 4. *AAE of Aks in combination with beta-blockers.*

Discussion

In 2020, within the framework of the European Congress of Cardiology (ESC), a new edition of the recommendations for the management of patients with AF was presented. Since 2000, the ESC has revised recommendations for the management of patients with AF six times. This circumstance is due to the social-economic significance of this pathology, on the one hand, and on the other hand, the accumulation of an extensive scientific and practical database based on the principles of evidence-based medicine, which requires systematization and analysis.

Despite the existing limitations in the recommendations for the use of Class Ic AADs in patients with severe organic myocardial changes, the drugs of this group are used with great efficiency in a large group of patients with no or minimal manifestations of organic myocardial disease.

It should be noted that, according to several experts, allapinin is conditionally assigned to the Class Ic of AADs. The conditionality of this classification is because the drug, in addition to a pronounced suppression of Na+ channels, also exhibits electrophysiological properties characteristic of AADs Classes III and IV. This feature of plant-derived AADs—the simultaneous detection (manifestation) of electrophysiological properties characteristic of different classes—has been described in recent publications. In this connection, it is logical to assume that Aks, as well as allapinin, being an herbal drug, may be devoid of side effects characteristic of the classic representatives of Class Ic, which are of inorganic origin, due to which Class 1c is generally contraindicated in organic heart diseases.

Herbal medicines, including AADs, have several advantages:

1. Most patients are ready to take natural medicines for a long time without fear. Standardized science-based natural substances cause fewer adverse effects and allergic reactions.

2. Allapin and Aks do not have a negative effect on the generation of an impulse in the sinus node and myocardial contractility, which is typical for artificial AADs. Allapinin and its derivatives are the drugs of choice in a number of clinical situations, in particular, arterial hypotension and bradycardia.

4. According to some scientists, the effect of a decrease in antiarrhythmic efficacy in long-term use of classical AADs is not very specific for AADs prepared from plant substances. At the same time, obtaining good results is possible only with standardization and strict quality control of phytodrugs.

Conclusion

The preventive efficacy of Aks (including in combination with BB) at a dose of 75-112.5mg/day in recurrent forms of AF is comparable to the “reference” drug Pr at a dose of 450-600mg/day. A decrease in the preventive efficacy of Aks is noted (86.7% and 80% after 1 month and 6 months of treatment, respectively), to a greater extent due to a decrease in the proportion of patients with absolute preventive efficacy.

Competing Interests

The authors declare that they have no competing interests.

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