Antiarrhythmic Activity of a Membrane-Protecting Agent Sal'magin in Rats with Aconitine-Induced Arrhythmias

A. A. Klekot

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Antiarrhythmic activity of a membrane-protecting agent Sal'magin was studied in rats with aconitine-induced cardiac arrhythmias. The test preparation was more potent than amiodaron in producing the antiarrhythmic effect in rats with Na^+-induced cardiac arrhythmias. The absence of side effects, low toxicity, and high animal survival rate under experimental conditions suggest that Sal'magin holds much promise as an antiarrhythmic drug in clinical practice.

Key Words: *antiarrhythmic drugs; Sal'magin; aconitine-induced cardiac arrhythmias; membrane protectors*

Therapy for cardiac arrhythmias is one of the most serious problems in cardiology. Antiarrhythmic drugs (AAD) are therapeutically effective only in 70% patients [1,4,7,9,10]. They cause various side effects, including the negative inotropic and intrinsic proarrhythmic effects. These features decrease the therapeutic value of AAD [4,6,7]. Class III AAD (classification of E. Vaughan-Williams and D. Harrison) are most often used in arrhythmology. They induce early post-depolarization and trigger activity of the myocardium. Overdosage is followed by polymorphous ventricular tachycardia of the "pirouette" type, which often results in ventricular fibrillation (VF, 85%) [4,10,11].

The development of effective and safe drugs is an urgent problem of modern arrhythmology. Membrane-protecting AAD hold much promise in this respect [2,9].

Impairment of the barrier and cation-transport functions of the plasma membrane plays an important role in the pathogenesis of cardiac arrhythmias. This disorder results in intracellular ion imbalance [3,5,8,13]. Any damage to the lipid bilayer of biological membranes and glycocalyx (polysaccharide complex on the outer membrane surface) promotes influx of arrhythmogenic cations into the cell and induces cardiac arrhythmias. It should be emphasized that arrhythmogenic ions enter the cell not only through ion channels, but also through pores in cardiomyocyte membrane. These pores are formed under the influence of various damaging factors at the micromolecular level. It is justified to use the drugs that increase plasma membrane density in cardiac cells and increase their resistance to damage.

Here we studied antiarrhythmic activity of a new membrane-protecting agent Sal'magin (magnesium salt of 2-hydroxybenzoic acid).

MATERIALS AND METHODS

Experiments were performed on 30 male and female laboratory rats weighing 170-200 g. The animals were intraperitoneally anesthetized with 35 mg/kg nembutal. ECG was recorded in standard lead II. Aconitine in a dose of 30 μg/kg was injected into the femoral artery to induce arrhythmias. The rats were divided into 3 groups of 10 specimens each. Group 1 animals served as the control. They received aconitine in the arrhythmogenic dose. Extrasystolic bigeminy was observed 2.5-4 min after aconitine infusion. Reference drug amiodaron

Vinnitsa National Medical University

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TABLE 1. Antiarrhythmic Effectiveness of Sal'magin in Rats with Aconitine-Induced Cardiac Arrhythmias

Group	Arrhythmias effect (sinus rhythm)				VF		Asystole		Survived	
	>3 min		>5 min							
	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%
1 (control)	0	0	0	0	9	90±10	9	90±10	1	10±3
2	1	10±3	1	10±3	6*	60±8	6*	60±8	4*	40±7
3	3	30±6	7	70±9	0	0	0	0	10*	100

Note. *$p<0.01$ compared to the control.

in a dose of 10 mg/kg (0.5% solution) was infused intravenously to group 2 rats exhibiting stable arrhythmia after aconitine administration. Group 3 animals with aconitine-induced cardiac arrhythmias received intravenous injection of 5% aqueous solution of Sal'magin in a dose of 100 μg/kg. Antiarrhythmic activity of drugs was estimated by stabilization of sinus rhythm and animal survival after aconitine infusion.

RESULTS

Activation of fast Na^+ channels with aconitine was followed by the development of cardiac arrhythmias in rats of all groups. It was manifested in ventricular extrasystoles or, more rarely, in atrial extrasystoles of the bigeminy type (3%, Table 1). Progression of cardiac arrhythmias in control animals resulted in VF, which caused asystole in 90% specimens.

Amiodaron was infused intravenously to group 2 rats with stable aconitine-induced arrhythmia. Sinus rhythm was restored in 20% animals. However, normalization of sinus rhythm was observed in only 1 rat (10%). By the end of study, 60% animals died from asystole due to VF.

In group 3 rats with Na^+-dependent arrhythmias, sinus rhythm was restored 10-15 sec after treatment with Sal'magin. However, restoration of sinus rhythm in 30% animals was short-lasting (less than 3 min) and followed by extrasystole. Repeated administration of Sal'magin was accompanied by a decrease in the number of ectopic complexes and restoration of sinus rhythm. Mortality was not observed in rats of this group.

These data indicate that Sal'magin is more potent than amiodaron in producing the antiarrhythmic effect (70%). The ineffectiveness of amiodaron in our study can be associated with the mechanism of its antiarrhythmic activity. Amiodaron mainly blocks K^+ channels, but has only a partial blocking effect on Na^+ channels. Na^+ ions continuously enter the cell through Na^+ channels upon treatment with aconitine. It should be emphasized that amiodaron has no effect on permeability of the lipid bilayer in membranes, which probably increases under the influence of cardiotoxins. Side effects of amiodaron were manifested in VF, which caused death of 60% rats. Hence, non-differential therapy with this drug is dangerous.

Sal'magin has a complex mechanism of action. Mg^{2+} cations activate Na^+/K^+-ATPase, which contributes to the exchange of intracellular Na^+ for extracellular K^+ and maintains resting potential of cardiomyocytes at the desired level. Nonspecific antiarrhythmic activity of Mg^{2+} is associated with antagonism to the physiological effect of Ca^{2+} and involvement in the regulation of metabolic processes and ATP synthesis. Another component of Sal'magin is the salicylic acid residue. Salicylates inhibit the synthesis and neutralize free radical oxygen species and lipid peroxidation products modulating permeability of cell membranes for arrhythmogenic cations (*e.g.*, Na^+ cations). The membrane-stabilizing effect on cells and subcellular structures is also associated with binding to biological membranes and decrease in their permeability. Therefore, this drug influences the major pathogenetic stage of Na^+-dependent cardiac arrhythmias.

Our results indicate that membrane-protecting agent Sal'magin is more potent than amidaron in producing the antiarrhythmic effect in rats with Na^+-induced cardiac arrhythmias. Sal'magin does not cause side effects, exhibits low toxicity, and is characterized by high survival rate of animals (100%). Hence, Sal'magin holds much promise as AAD in clinical practice.

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