Antiarrhythmic Activity of Taurhythman

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Antiarrhythmic properties of taurhythman were demonstrated on experimental models of ventricular (early occlusion and calcium chloride-induced) and atrioventricular (aconitine-induced) arrhythmias. The preparation reduced or prevented episodes of paroxysmal tachycardia and ventricular fibrillation, decreased the incidence of arrhythmias, and increased the lethal dose (LD) of arrhythmogenic agents. By its efficiency, taurhythman was superior to procainamide and comparable to lidocaine.

Key Words: *taurhythman; lidocaine; procainamide; arrhythmias*

Taurhythman (isopropylamide N-(1-methyl-2-phenylethyl)aminoethane sulfonic acid hydrochloride) is a novel cardioprotective preparation with pronounced antihypoxic, antiischemic, and hypotensive effects. Our aim was to study the antiarrhythmic potency of taurhythman on rats with heart rhythm disturbances of various geneses.

MATERIALS AND METHODS

The experiments were carried out on random-bred male albino rats (n=90) weighing 220-250 g from Rappolovo Animal Breeding Center (Russian Academy of Sciences).

The antiarrhythmic activity of taurhythman, lidocaine, and procainamide was evaluated on models of ventricular arrhythmias including early postocclusion arrhythmia including fibrillation [5], calcium chloride-induced arrhythmia [1], and aconitine-induced atrioventricular arrhythmia [2].

Activity of antiarrhythmics in early postocclusion arrhythmia was assessed by the incidence of heart rhythm disturbances (HRD) and by their severity (number of ventricular extrasystoles, duration of episodes of ventricular tachycardia and ventricular fibrillation) during 30-min monitoring [6].

Non-ischemic HRD were induced by intravenous infusion of calcium chloride (14 mg/min) or aconitine (0.01 mg/min) until cardiac arrest documented by continuously recorded ECG. The infusion period varied for various animals from 5 to 10 min. The doses of calcium chloride or aconitine that caused HRD and asystole were then calculated.

Taurhythman, lidocaine, and procainamide were administered as a single bolus injection (10 mg/kg) immediately after occlusion or just before arrhythmogenic infusion with subsequent continuous infusion to the end of the experiment at a rate of 0.05 mg/kg×min.

The control animals received physiological saline (intravenous 0.2-ml bolus and infusion at the rate of 0.05 ml/min).

The results were analyzed statistically using Statgraphics software and Student's t test.

RESULTS

In all control rats, occlusion of the left coronary artery provoked early arrhythmias (single or grouped ventricular extrasystoles) and ventricular tachycardia paroxysms, which developed within 4-25 min after occlusion (Table 1). In 80% control rats, ventricular fibrillation was documented, which in one case led to cardiac arrest.

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The development of the early postocclusion HRD proceeded in two phases. Phase 1a lasted for the first 10 min after occlusion. It was caused by pronounced conduction disturbances in ventricles and by delayed activation of subepicardial structures of the myocardium, where arrhythmias (usually, of the re-entry type) appeared [4,5]. Phase 1b started after minute 12 and reached maximum on minutes 15-18. It probably resulted from catecholamines release (which was most active on minutes 15-30 of ischemia) and related to enhanced automaticity of the latent centers or trigger activity in the deep layers of the myocardium [3].

Lidocaine had no effect on the incidence of extrasystoles, but almost 4-fold decreased their number (Table 1). Ventricular tachycardia and fibrillation did not develop in rats treated with lidocaine. All animals of this subgroup survived to the end of the experiment. In addition to pronounced decrease of arrhythmia severity during the first 10 minutes after occlusion of the coronary artery (1a), lidocaine completely prevented HRD during 12-30 (1b) min by impeding re-entry and blocking the foci of ectopic automaticity and/or trigger activity.

Taurhythman exerted similar effects. It decreased the number of ventricular extrasystoles 3-fold and significantly decreased the incidence and severity of ventricular tachycardia. Similarly to lidocaine, it prevented ventricular fibrillation, HRD in phases 1a and 1b, and animal death.

Intravenous infusion of calcium chloride in all cases provoked bradycardia followed by inhibition of sinoatrial node and appearance of substitution rhythms accompanied by ventricular flutter and fibrillation and cardiac arrest. As a rule, flutter and fibrillation replaced each other and were observed in 80% control rats. In other 20% cases (2 of 10 rats) asystole appeared against the background of pronounced bradyarrhythmia accompanied by substitution of the sinus rhythm.

Lidocaine or taurhythman administered simultaneously with calcium chloride decreased the incidence of ventricular flutter and fibrillation to 30% and 40%, respectively, and increased the doses of calcium chloride provoking conduction disturbances (to 237±16 and 264±11 mg/kg, respectively, *vs.* 111±10 mg/kg in the control) and inducing ventricular arrhythmias (to 504±10 and 495±12 mg/kg, *vs.* 436±18 mg/kg) and cardiac arrest (to 536±20 and 529±20 mg/kg, respectively, *vs.* 481±21 mg/kg). The antiarrhythmic effect of taurhythman was comparable to that of lidocaine.

Intravenous infusion of aconitine to control rats induced supraventricular tachycardia and atrial extrasystoles in 1-2 min after the start of infusion, which were followed by ventricular rhythm disturbances such as extrasystoles, tachycardia, flutter and fibrillation terminated by cardiac arrest (Table 2).

When procainamide or taurhythman were infused simultaneously with aconitine, they significant-

TABLE 1. Effect of Test Preparations on Early PostOcclusion HRD during Acute Myocardial Infarction in Rats

Group	Ventricular extrasystoles		Ventricular tachycardia		Ventricular fibrillation	
	number	incidence, %	duration, sec	incidence, %	duration, sec	incidence, %
Control	523±2	100	184±16	100	25±4	80
Lidocaine	134±9*	100	0*	0*	0*	0*
Taurhythman	171±12*	100	11±5*	20*	0*	0*

Note. Here and in Tables 2 and 3: *$p<0.05$ compared to the control.

TABLE 2. Effect of the Tested Preparations on HRD Provoked by Intravenous Infusion of Aconitine in Rats (n=10)

Arrhythmia type	Control		Procainamide		Taurhythman	
	abs.	%	abs.	%	abs.	%
Supraventricular tachycardia	8	80	4	40*	3	30*
Atrial extrasystole	9	90	4	40*	5	50*
Ventricular extrasystole	10	100	6	60*	5	50*
Ventricular tachycardia	10	100	7	70*	6	60*
Ventricular flutter	10	100	6	60*	6	60*
Ventricular fibrillation	10	100	4	40*	5	50*

TABLE 3. Calculated Aconitine Doses Evoking Arrhythmia and Cardiac Arrest in Rats Treated with Antiarrhythmics (*M*±*m*, mg/kg)

Arrhythmia type	Control	Procainamide	Taurhythman
Supraventricular tachycardia	27.0±1.6	48.3±2.1*	51.4±2.9*
Atrial extrasystoles	38.5±2.4	71.6±3.1*	74.5±3.8*
Ventricular extrasystoles	45.6±1.9	87.0±2.8*	79.1±2.7*
Ventricular tachycardia	63.9±4.5	137.3±8.6*	116.5±7.6*
Ventricular flutter	84.4±9.3	158.8±10.2*	134.1±9.4*
Ventricular fibrillation	139.0±10.4	174.5±12.8*	164.1±10.2*
Asystole	192.7±18.4	275.9±21.3*	244.7±19.4*

ly diminished the incidence of supraventricular and ventricular arrhythmias. Moreover, these agents increased the doses of aconitine provoking HRD and asystole (Table 3).

Thus, our experiments demonstrated pronounced antiarrhythmic effects of taurhythman. This effect manifested during ventricular HRD induced by occlusion of the left coronary artery or by infusion of calcium chloride and during atrioventricular arrhythmias provoked by aconitine. In all HRD models used in this study, antiarrhythmic activity of taurhythman was comparable to that of lidocaine and procainamide. The potency of taurhythman to moderate or prevent paroxysmal tachycardia and ventricular fibrillation, to diminish the incidence of HRD, and to increase LD of arrhythmogenic agents can be explained by antihypoxic and membrane stabilizing properties of this potent agent.

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