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Research Article

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2-aminoaethanesulfonic acid compounds possess protective property in reperfusion-induced heart jnjury

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Abstract

The study aim was to explore pharmacological effects of 2-aminoaethansulfonic acid compounds in reperfusion-induced heart injury.

Materials and methods. The study was performed on rats and dogs of both sexes, isolated rats' hearts. Two compounds of 2-aminoethanesulfonic acid, magnesium-containing (LBK-527) and phenylacetamide-containing (LKhT-317) were investigated. Antiarrhythmic effects of the compounds were studied in coronary artery reperfusion 7, 30 and 120 min after acute myocardial ischemia modeling. The ability of the substances to limit the volume of reperfusion injury was investigated by differential indicator method. The influence of substances on the intensity of free radical processes in the myocardium, as well as the metabolic profile of coronary venous blood during reperfusion, was studied. Hemodynamic effects of the substances were studied during in vivo experiments, as well as on an isolated heart.

Results and discussion. The compounds effectively prevent cardiac arrhythmias generation caused by myocardial reperfusion after 7, 30 and 120 minutes of ischemia. Prophylactic intravenous administration of LHT-317 and LBK-527 at higher therapeutic doses limit the size of rats' heart necrosis zone after occlusion-reperfusion syndrome develops, prevent reperfusion-induced excessive activation of free-radical processes in rat myocardium, activate the antiradical activity of the heart tissues, and optimize [O_2] and [CO_2] in coronary venous sinus blood of dogs. Cardioprotective effect of the compounds manifests in preserving myocardium contractile function, maintaing BP and stabilizing heart chronotropic function.

Conclusions. The study analysis shows that 2-aminoethanesulfonic acid compounds have cardioprotective effect in reperfusion syndrome.

Keywords

ischemic and reperfusion heart injury, 2-aminoaethanesulfonic acid compounds, arrhythmia, hemodynamics, lipid oxidation, metabolic profile, isolated heart.

Introduction

Acute occlusive and reperfusion-induced myocardial injury is the dominant cause of death of patients with coronary heart disease (Chin et al. 2015). Arising from the coronary artery recanalization, reperfusion syndrome is manifested by the development of cardiac arrhythmias, cardiomyocytes death, and heart failure (Wit and Janse 2001). The most typical clinical situations that create the prerequisites for the development of reperfusion syndrome in cardiology are acute myocardial infarction with ST-segment elevation on the ECG due, as a rule, to thrombosis at the site of atherosclerotic plaque rupture, interventional cardiac surgeries, coronary artery bypass grafting and heart transplantation (Yellon and Hausenloy 2007).

Early reperfusion of ischemic myocardium seems to be a key event for maintaining the vital activity of myocardial tissue and improving the clinical outcomes of an acute ischemic coronary disaster (Yellon and Hausenloy 2007). Paradoxically, as a result of the aforementioned reperfusion strategy, subsequent deterioration of tissue, cellular and subcellular structures of the myocardium is more pronounced than that observed only due to acute ischemia, with the formation of the so-called reperfusion syndrome.

It was first described in 1960 by Jennings, who observed myocardial damage due to its reperfusion after a period of acute ischemia in dogs with swelling of cardiac cells, contracture of myofibrils and calcification of mitochondria of cardiomyocytes. Later, it was proved that the reperfusion strategy induced death of the viable cardiomyocytes in ischemic zone and increased the size of infarction (tissue death). Moreover, the authors found that at least 50% of the final dimensions of the necrosis area was due to the reperfusion injury of heart tissue. Thus, it was shown that pharmacological intervention during the reperfusion period aimed at preserving the vital activity of the ischemic myocardium seemed to be a realistic scenario in terms of the possibility of limiting the size of organ damage (Karwi et al. 2018).

However, despite numerous experimental studies of various pharmacological approaches to the prevention and treatment of reperfusion syndrome, up to now there is no strategy with proven clinical efficacy (Chin et al. 2015).

Currently, it is believed that the key elements of reperfusion injury of internal organs are overproduction of reactive oxygen intermediates, cell overloading with Ca^{2+}, tissue inflammatory cells infiltration. In the myocardium, this leads to the formation of pharmacoresistant reperfusion arrhythmias, stunning, microcirculatory dysfunction, hemodynamic disorders, and death of cardiomyocytes (Maxwell and Lip 1997).

Now numerous promising molecules of drugs are being studied with a high potency to have cardioprotective, antiischemic and antiarrhythmic properties, to correct endothelial dysfunction in order to normalize regulation of vascular pressure and microcirculatory blood flow (Blinova et al. 2016, Vasilkina et al. 2016, Shakhno et al. 2018, Pokrovskii et al. 2017). Among the substances of the kinds, our attention was drawn to salts of 2-aminoethanesulfonic acid containing magnesium and dimethylphenylacetamide as a base. These compounds were chosen to study the possibilities of preventive effects on the myocardium with the purpose of developing a pharmacological strategy to prevent reperfusion injury of the heart, which is a major challenge of pharmacology.

Materials and methods

All the study protocols were reviewed and approved of by the Local Ethics Committee of Ogarev Mordovia State University (Protocol No. 10 of October 21, 2015).

Animals and biological materials

The study was carried out in 174 non-linear white rats of both sexes with the initial weight of 180-220 g, obtained from "Andreevka" Animal Husbandry Facility (Russia) and 20 mongrel dogs of both sexes weighing 10.0-15.0 kg. The animals were maintained in a special facility of The Center for Advanced Studies of Innovative Medicines of Ogarev Mordovia State University under the conditions which met all the requirements of National Standard of the Russian Federation "Principles of Good Laboratory Practice".

All the painful procedures and manipulations were performed under general anesthesia. Barbiturate anesthesia (thiopental sodium intravenously/intrapleurally) or ethereal anesthesia (ether for anesthesia inhalation by using TOPO Small Animal Ventilator, Kent Scientific, USA) was used.

Substances and drugs

In the study, two original substances – chemical compounds containing the residue of 2-aminoethanesulfonic acid, synthesized at the Department of Chemistry and Synthetic Drugs Technology of All-Union Research Center for Safety of Biologically Active Substances (Russia) – were used. Figure 1 shows the chemical structures of the compounds: 2-(diethylamino)-N-(2,6-dimethylphenyl)-acetamide 2-atsetaminoetansulfonoate (laboratory code LKhT-317) and Magnesium bis-acetaminoethanesulfonate (laboratory code LBK-527). LKhT-317 is white fine crystalline powder, highly soluble in water, odorless or with a slight smell of hydrogen sulfide. LBK-527 is white crystalline powder that is highly soluble in water, without smell.

At all stages of the study, in order to obtain objective results, reproducible experimental models and to identify the advantages, reference medications at isotoxic doses that were equivalent to those of the tested substances. Reference medications used were as follows: 1) Lidocaine hydrochloride (officinal liquid dosage form "Lidocaine", injection solution, 20 mg/ml, 2 ml, ampouled, manufactured by "Egis" (Hungary), series No. T111A1014, exp. date 10.2019); 2) Amiodarone (officinal liquid dosage

form "Kordaron", solution for intravenous administration, 50 mg/ml, 3 ml, ampouled, manufactured by "Sanofi Aventis – FRANCE" (France), series No. 6A011, exp. date 01.2018); 3) Verapamil (officinal liquid dosage form "Verapamil", solution for intravenous administration, 2.5 mg/ml, 2 ml, ampouled, manufactured by "Alkaloid AO" (Republic of Macedonia)), lot 0716 No 98836, exp. date 07.2019); 4) Propranolol (officinal liquid dosage form "Obzidan", 0.1% solution for intravenous administration, 5 ml, ampouled, manufactured by "Isis Pharm GmbH" (Germany), series 05x 11178, exp. date 12.2017).

The highest clinical dose (HTD) administered in all the experiments and for all the types of laboratory animals did not exceed 5% of the LD_{50} value determined for mice for the tested administration route.

The calculation of the dose for dogs and rats was carried out taking into account the rules of interspecific re-estimation from the dose of mice (Freireich et al. 1966). To determine the accumulated effective dose (AED) in experiments in dogs, the infusion of the substances was performed, but no more than before reaching HTD.

Experimental methods

The antiarrhythmic effect of the compounds under the conditions of reperfusion arrhythmia was studied in the experiments on rats on the models of transient ischemic attacks and reperfusion arrhythmias and reperfusion heart rhythm disturbances induced by ischemic heart stimulation of rats, as well as in experiments when reper-

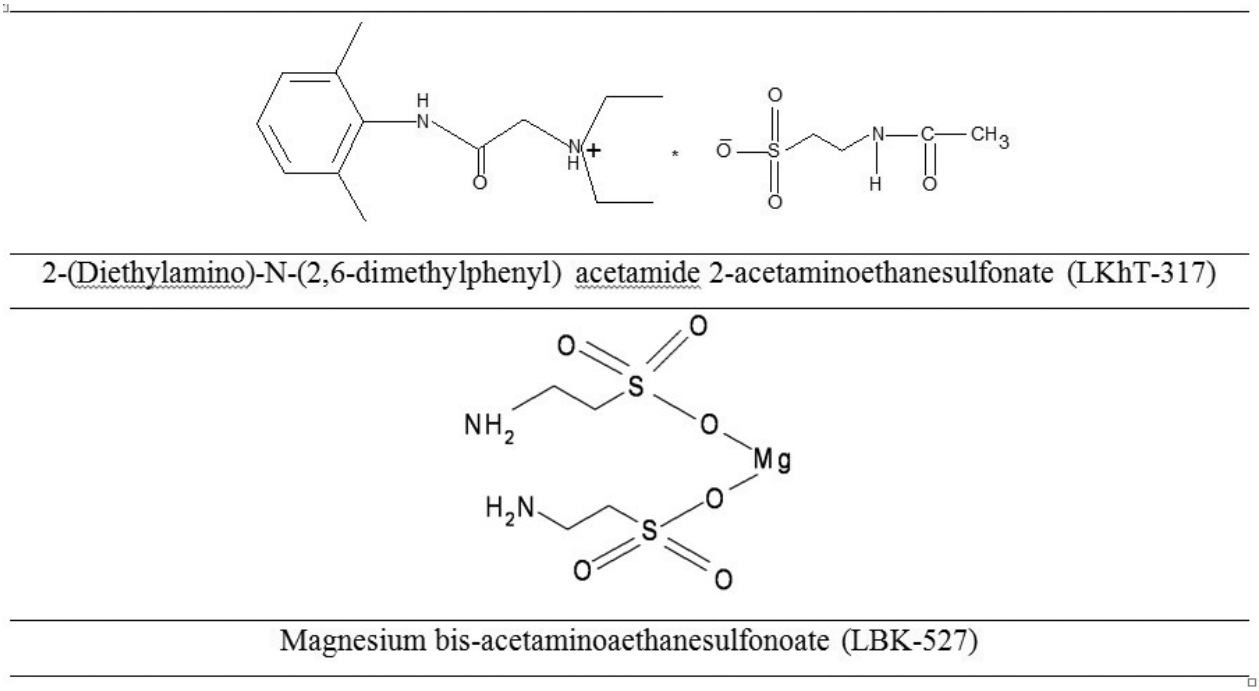

Figure 1. Chemical structures of 2-aminoaethanesulfonic acid compounds

fusion was reproduced 120 min after ischemia onset in dogs (Milan and MacRae 2005). To determine the size of heart ischemia and necrosis, the differential indicator method by Sernov and Gatzura (1989) was used, in our modification allowing reperfusion of the myocardium 120 minutes after an acute ischemia onset. The intensity of lipid peroxidation processes and the antiradical potency of myocardial tissue was studied by chemiluminescent method using Emilit EL photometer (USA). The impact of the tested compounds on some metabolic parameters was determined by the concentration levels of oxygen, carbon dioxide, pH, the capacity of carbonate buffer in dogs' coronary venous sinus blood by using EasyBlood-Gaz analyzer (USA). The hemodynamic effects of LKhT-317 and LBK-527 were studied in a non-invasive manner (two-channel CODA system, Kent Scientific, USA). The contractile activity of the left ventricle during the ischemia/reperfusion period was determined by recording the dP/dt_{max} rate by means of a blood pressure (BP) transducer ("Ugo Basile", Italy) and a recorder by the same manufacturer. The effect of the compounds on the volume of outflowing perfusate and an isolated heart survival time was studied in the hypoxic/reoxygenated rats' hearts by Langendorff method (Takeo et al. 1988).

The statistic significance of the obtained results was estimated with modern statistics methods using licensed PC interface "BioStat", SPSS and PC iMac Retina (USA).

Results and discussion

The efficacy of the substances on the model of late reperfusion arrhythmia was studied in dogs under the circumstances of coronary artery recanalization performed

2 hours after the development of acute ischemia. The methodical technique allowed determining AEDs of the tested substances, reaching which either completely suppressed arrhythmia, or reduced the ectopic activity by more than 50%. It was determined that the AED of LKhT-317 was greater than that of lidocaine, but lower than that of amiodarone (Figure 2). Unlike amiodarone, LKhT-317 brought about complete antiarrhythmic effect, but unlike lidocaine hydrochloride, the duration of the antiarrhythmic action of the substance was significantly higher. The magnesium-containing derivative of 2-aminoethanesulfonic acid (LBK-527) had the lowest antiarrhythmic effect among all the pharmacological substances studied: no cases were recorded of complete suppression of ectopic activity. However, it should be stressed that the achievement of a partial antiarrhythmic effect in all animals was observed with the administration of a total dose of the substance not exceeding 50% of HTD. It is also noteworthy that the duration of the substance action was significantly higher than that of lidocaine, but inferior to that of amiodarone.

The model of early reperfusion arrhythmia in rats made it possible to study the prophylactic effectiveness of administering the tested compounds intravenously to restore coronary blood flow after a relatively short period of acute ischemia - 7 minutes (Figure 2). So, in this model, the optimal administered dose of LKhT-317 can be considered 4.2 mg/kg, at which the substance showed a full antiarrhythmic and antifibrillatory effects. As for the peculiarities of pharmacodynamics of LBK-527 on the model described, it should be emphasized that, like on the late reperfusion model, the antiarrhythmic activity of the substance was less pronounced than that of LKhT-317. At a dose of 50% of HTD, the compound showed no activity at all. An increase in the dose to reach HTD resulted in a milder effect in comparison with that of the reference medications.

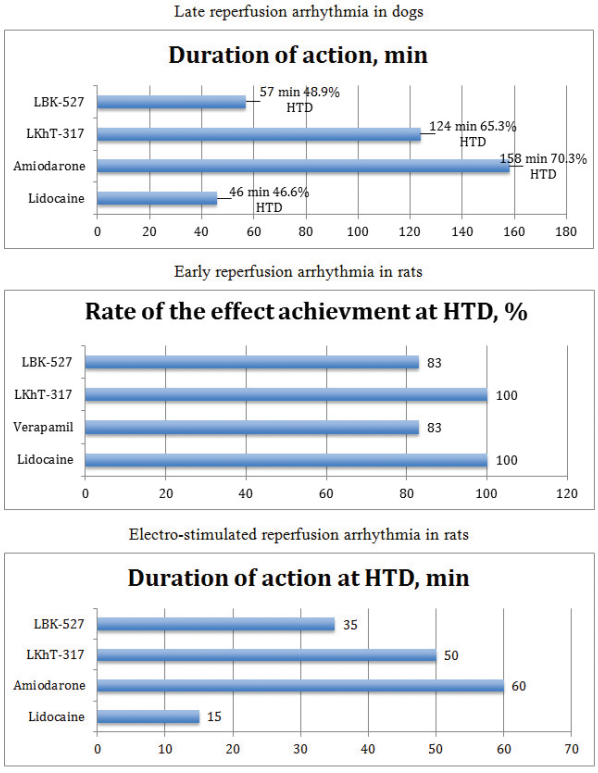

Figure 2. Comparison of the antiarrhythmic action of compounds by duration and/or rate on different reperfusion-induced arrhythmia animal models

Unlike the aforementioned models of reperfusion rhythm disorders, the model of electro-stimulated arrhythmia is based on a fundamentally different approach. Firstly, the duration of the ischemia period is 30-35 min, the time during which the irreversible processes of cell death of the most ischemia-affected myocardium zones can start in animals. Secondly, rhythm disturbances are generated actively by electrical stimulation, thus creating a more aggressive pathological environment, allowing a more objective assessment of the antifibrillatory efficiency of the potential drugs.

Pharmacologucal effect of the tested compounds on this model is characterized, first, by LKhT-317 having antifibrillatory action, which is comparable with that of amiodarone, and, secondly, in comparison with lidocaine the compound action duration increases up to 30-35 min of observation (Figure 2). Magnesium-containing 2-aminoethanesulfonic acid derivative (LBK-527) also has antifibrillatory action on the model of electrical stimulation of myocardium during reperfusion, however, by the preventing action intensity, the compound is significantly inferior to the derivative of LKhT-317 and the reference drug – amiodarone. Both compounds are more active than lidocaine.

The most favorable scenario for development of occlusion-reperfusion syndrome is ischemic preconditioning, which allows the cellular structures of the ischemic myocardium to rearrange for an optimal mode of energy production and oxygen consumption (Murphy and Steenbergen 2008).

Using a differential indicator method for determining the size of ischemia and necrosis zones rats' hearts with reperfusion syndrome (Table 1), it was determined that intravenous administration of LKhT-317 is accompanied by a reduced volume of irreversible damage to the heart muscle, comparable to that when administering propranolol and amiodarone. At the same time, LKhT-317 did not reduce the size of the ischemic zone. The efficacy of the second tested compound – a magnesium-containing derivative of 2-aminoethanesulfonic acid LBK-527 – was the smallest among all medications investigated. Reduction in the size of the necrosis zone caused by the compound was statistically significant when compared with that in the control, but it was smaller in comparison with the other substances.

Thus, magnesium and phenylacetamide-containing salts of 2-aminoethane-sulfonic acid have a cardioprotective effect in myocardium reperfusion injury, which manifests itself in limiting the volumes of irreversible myocardial damage. Consequently, it can be assumed that substances can transfer the hearts of animals to a state of ischemic

Table 1. Impact of LBK-527 and LKhT-317 on the volume of injured myocardium in rats with post-ischemic reperfusion syndrome

Drug (Compound)	Dose mg/kg	n	Necrosis share of total weight of the myocardium (%)	Ischemia share of total weight of the myocardium (%)	Ratio of the ischemic zone size to the necrosis zone size, %
Control no. 1	–	6	45.4±2.0	22.2±1.6	49.6±4.4
Control no. 2	–	6	36.8±1.8[a]	20.4±2.1	56.5±2.0
Amiodarone	28.5	6	31.5±2.2*	20.2±1.4	64.1±2.3*
Propranolol	0.8	6	28.1±1.1*	21.2±1.2	75.4±2.6*
LBK-527	15.0	6	30.3±1.2*	20.7±1.6	68.3±1.4*
LKhT-317	4.2	6	31.7±1.8*	20.8±1.8	65.6±1.8*

Note: * in comparison with control no. 2, differences are statistically significant at p<0,05; [a] in comparison with control no. 1, differences are statistically significant at p<0,05 (one-dimension dispersion analysis; Newman-Keuls criterion)

preconditioning, which is the most favorable mechanism of adapting to ischemic and reperfusion syndrome.

Assessment of the state of metabolic processes in the myocardium under reperfusion conditions is an important component of studying the role of potential drugs in the prevention and correction of heart reperfusion injury. Reoxygenation of tissues in ischemia entails the activation of oxygen-dependent enzyme systems with sometimes dramatic consequences for cells and tissue in general. In experiments on dogs in which after 30 min of occlusion, reperfusion injury of the heart was reproduced for 15 min, partial oxygen and carbon dioxide pressure and saturation, pH, and the capacity of the carbonate buffer system were studied. The compounds under study effectively prevented the pathological shifts of the homeostatic indices of blood flowing from the myocardium damaged zone: there was correction of ischemic acidosis and of gas pressure in blood, indicating the formation of an optimal mode of oxygen consumption by the myocardium. It should be noted that both compounds, but LKhT-317 to a greater extent, were active in preventing the negative consequences of reperfusion, rather than of ischemic damage.

Numerous studies conducted recently in the world have shown that the use of protocols that inhibit the development of lipid peroxidation and the active oxygen intermediates inducing its release leads to a significant weakening of the damaging effect of reperfusion on cardiac tissue. When studying intravenous administration of magnesium salt of 2-aminoethanesulfonic acid (LBK-527) at HTD, a protective effect on the processes of lipid peroxidation induced by reperfusion was revealed (Table 2). The intensity of the lipid peroxidation decreased whereas antioxidant activity increased, but its values did not reach the level of peroxidation activity at the affected area of the myocardium. In contrast, administration of LKhT-317 as a heart-protector along with a decrease in the level of lipid peroxidative process proportionally intensified the antioxidant activity of heart tissue, repeating the pharmacological effect of reference medication verapamil.

Possibly the established activity of LKhT-317 may be related to the proven ability of dimethylphenylacetamide and some of its derivatives to inhibit lipid peroxydation processes and to activate protective reactions in heart of animals under experimental conditions (Yakya et al. 2018).

Untimately, ischemic and reperfusion heart injury leads to the death of part of parenchymal cells of the organ, violations of the contractile function and electrophysiological changes that result in electrical instability of the

Table 2. General antyperoxidant activity and intensity of free-radical lipoperoxidation in rats' myocardium after reperfusion and iv administration of 2-aminoaethanesulfonic acid compounds (M±SD)

Attack intensity, imp/sec	Drug, dose (mg/kg)	Measuring point		
		LA	LV RZ	LV IZ
Lipid peroxidation	Control no.1	4.5±0.6	9.7±0,5	8.9±0.7
	Control no.2	5.1±1.2	12.2±1.8	67.4±4.7[a]
	LBK-527, 15.0	4.8±0.8	11.3±1.1	42.1±2.4*
	LKhT-317, 4.2	5.0±0.6	10.9±0.9	38.6±4.2*
	Verapamil, 1.7	4.9±1.2	12.0±1.3	32.5±3.1*
Antioxidant activity	Control no.1	4.8±0.5	10.1±1.0	10.2±0.8
	Control no.2	5.3±0.9	6.7±0.7	23.4±3.6[a]
	LBK-527, 15.0	4.5±0.8	7.8±1.4	32.6±2.7*
	LKhT-317, 4.2	5.4±1.2	8.6±1.5	38.7±3.8[f]
	Verapamil, 1.7	4.7±0.7	8.9±2.5	36.4±2.5[f]

Note: RZ LV – remote zone of left ventricle; IZ LV – intact zone of left ventricle; LA – left atrium. * in comparison with control no. 1, differences are statistically significant at p<0.05; [a] in comparison with control no. 1, differences are statistically significant at p<0,05;[f] in comparison with control no. 1 and control no. 2, differences are statistically significant at p<0,05 (One-dimension dispersion analysis; Newman-Keuls criterion)

myocardium, the dysfunction of its rhythmic activity, and the generation of cardiac rhythm disturbances. Therefore, at the final stage of the study, the effect of prophylactic administration of 2-aminoethanesulfonic acid compounds on the hemodynamics of the animals with experimental reperfusion syndrome and the bioelectrical activity of an isolated heart was evaluated. LKhT-317 showed most significant cardioprotective properties preventing hemodynamic disorders. Its preventive intravenous administration at a dose of 4.2 mg/kg did not affect the ischemic period of the experiment. However, the severity of the reperfusive hemodynamic shifts was obviously lower than that in the control: the compound prevented a negative inotropic reperfusion effect, as well as a critical stagnation of blood pressure. At the same time, both compounds favorably influenced the hemodynamic consequences of reperfusion syndrome, which showed in the prevention of contractility and BP functions. The results obtained can be explained by the ability of compounds to prevent excessive activation of lipid peroxydation, optimization of metabolic processes in the myocardium, and antiarrhythmic properties of LBK-527 and LKhT-317.

In the experiments in Langendorff isolated rat's heart, global hypoxia/reoxygenation was reproduced (Figure 3). During 15 minutes of global cardiac hypoxia, the progressive extinction of the bioelectric and pumping functions of the organ was observed, which showed in a decrease in heart rate on average from 40 to 27 beats per min. and a decrease in the rate of perfusate outflow by 30% of the initial level.

Reoxygenation performed on the 15th minute of the experiment led to a short-term and incomplete recovery of both the rhythm frequency and the volume indices of the intracardiac dynamics of the perfusion solution, but by the final phase of observation, the bioelectrical activity of the isolated heart faded.

The magnesium-containing salt of 2-aminoethanesulfonic acid (LBK-527) at a concentration of 10^{-4} M had practically no effect on the performance of the isolated heart during the hypoxia period, but it stimulated a more efficient recovery of the lost functions of the organ during the reoxygenation, which showed in a significant, in comparison with the control group, increase in heart rate, measured at 30 and 45 minutes of the experiment and in volume indices of intracardiac hemodynamics. Even more contrasting results were obtained against the background of perfusion of the isolated heart with the Krebs-Hanseleit solution containing LKhT-317 in the same concentration: the heart rate, the rate of perfusate outflow were restored, and the volume of the outflowing perfusate was maintained at a high level. The results obtained indicate a high protective function of the compounds under conditions of hypoxia/reoxygenation of isolated heart.

Thus, the experimental study analysis showed that 2-aminoethanesulfonic acid compounds have cardioprotective activity in reperfusion syndrome. LKhT-317 and LBK-527 at therapeutic doses effectively prevent the formation of reperfusion rhythm disorders after 7-, 30- and 120-minute of acute ischaemia. Preventive administration of the substances limits the activation of lipid peroxidation processes in the myocardium, optimizes oxygen consumption during reperfusion, which reduces the size of the infarction zone by 20-25% when compared with those in the animals in the control group. Modulation of metabolic homeostasis leads to weakening the manifestations of electrical instability of the myocardium, as well as maintaining its contractility at a level sufficient to maintain hemodynamic stability.

Conclusions

According to the obtained data, the following conclusions were made:

1. Magnesium-containing (LBK-527) and phenylacetamide-containing (LKhT-317) 2-aminoethanesulfonic acid compounds effectively prevent the generation of cardiac arrhythmias caused by myocardial reperfusion of animals' heart after 7, 30 and 120 minutes of ischemia.

2. Prophylactic intravenous administration of LKhT-317 and LBK-527 at higher therapeutic doses limit the size of rats' heart necrosis zone after occlusion-reperfusion syndrome develops and are as effective as the reference medications amiodarone and propranolol.

3. The tested compounds prevent reperfusion-induced excessive activation of free-radical processes in rat's myocardium; activate the antiradical activity of the heart tissues. Their intravenous injection before coronary artery occlusion is followed by optimization of oxygen and carbon dioxide partial pressure in coronary venous sinus blood of dogs, acidosis correction in response to the restoration of blood flow through the coronary arteries.

4. Cardioprotective effect of LBK-527 and LKhT-317 in experimental reperfusion syndrome shows in preserving the myocardium contractile function, maintaining BP and stabilizing heart chronotropic function.

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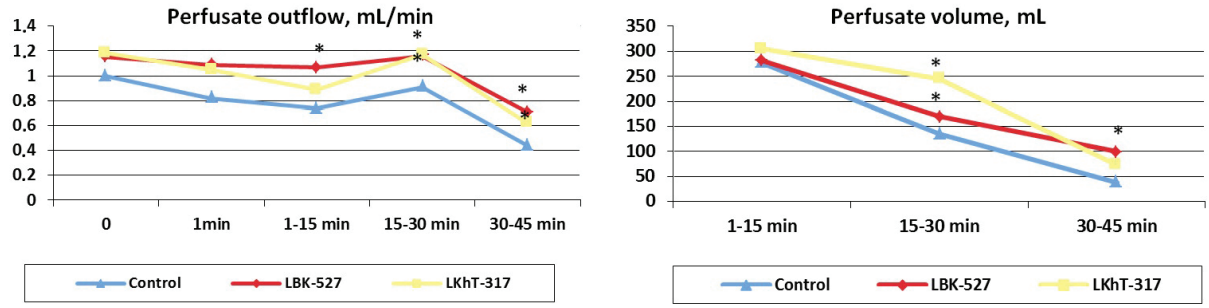

Figure 3. Dynamics of perfusate outflow rate and and of total volume of outflowing perfusate over 15 minutes of experiment (V_{total}) when administering LBK-527 and LKhT-317 *Note:* * in comparison with control, differences are statistically significant at p<0,05 (One-dimension dispersion analysis; Newman-Keuls criterion) (M±SD)

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