PHARMACOLOGY AND TOXICOLOGY

Effect of Compound LBK-149 on Antiarrhythmic Activity of Lidocaine in Rats with Arrhythmias and Disturbances in Lipid and Carbohydrate Metabolism

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Antiarrhythmic activity of lidocaine during early occlusion and reperfusion arrhythmias decreased in rats with experimental disturbances in lipid and carbohydrate metabolism. The course of additional treatment with compound LBK-149 potentiated antiarrhythmic activity of lidocaine.

Key Words: *lidocaine; compound LBK-149; arrhythmias*

The development of arrhythmias and conduction disturbances is one of the most serious complications of coronary heart disease (CHD). These abnormalities often become the major and sometimes the only sign of the disease and determine its prognosis. The use of antiarrhythmic drugs for the therapy of ventricular arrhythmias in patients with organic heart diseases is a complex problem, which has contradictory aspects. These drugs have several serious contraindications and cause a variety of side effects [2,7].

The toxic effect of antiarrhythmic drugs and their proarrhythmogenic activity in patients with arrhythmias induced by ischemic/reperfusion injury to the myocardium can be associated with metabolic disturbances and electrolyte imbalance accompanying CHD [6]. Lipid peroxidation (LPO) and cytotoxic effect of free radicals play an important role in the pathogenesis of these disorders [5]. Metabolic disturbances in the organism modulate the kinetics of antiarrhythmic drugs, which creates prerequisites for overdosage and toxic influences on the myocardium manifesting in spontaneous arrhythmias and impaired myocardial contractility, which can be the cause of sudden death [4]. These data provide the theoretical basis for the use of antioxidant drugs in combination antiarrhythmic therapy of heart rhythm disorders during CHD [3].

The antiarrhythmic effect (AAE) of lidocaine during experimental early occlusion (EOA) and reperfusion arrhythmias (RPA) was studied in rats with disturbances in lipid and carbohydrate metabolism accompanied by LPO activation. We also evaluated the possibility of correcting AAE of lidocaine by additional treatment with compound LBK-149.

MATERIALS AND METHODS

Experiments were performed on 60 male and female outbred albino rats weighing 180-200 g. The animals were intraperitoneally narcotized with sodium thiopental in a dose of 40 mg/kg. The study was conducted on the model of EOA and RPA. ECG was recorded in standard lead II during 30-min occlusion and 10-min reperfusion. Changes in heart rate (HR), incidence of ectopic contractions, ventricular extrasystoles, ventricular tachycardia, ventricular fibrillation, and conduction disturban-

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ces, and initiation and duration of arrhythmias were evaluated.

Experimental arrhythmias were also studied under conditions of disturbances in lipid and carbohydrate metabolism (alloxan-cholesterol dyslipidemia). This condition was modeled by single intraperitoneal injection of alloxan (135 mg/kg) and daily treatment with oil solution of cholesterol (40 mg/kg, 30 days) [1]. This model reflects the imbalance between lipid fractions, which is similar to type IIB dyslipidemia (WHO classification). The disorder is characterized by hyperlipidemia, hypertriglyceridemia, increased atherogenicity index, and hyperglycemia. These changes were accompanied by LPO activation in the heart and plasma.

Lidocaine (2% solution, 10 mg/kg) was injected intravenously 2-3 min before the start of arrhythmias to prevent heart rhythm disturbances.

Compound LBK-149 (laboratory code) is a low toxic derivative of 5-hydroxynicotinic acid synthesized at the Laboratory of Bioregulators (All-Russian Research Center for Safety of Bioactive Substances). This compound exhibits high antioxidant and antiischemic activities. LBK-149 was injected intramuscularly in a single daily dose of 25 mg/kg (0.5% LD_{50}) over the last 10 days of the study.

We calculated the mean values and standard errors. The significance of differences was evaluated by Student's t test and χ^2 test (5% significance level).

RESULTS

Lidocaine exhibited AAE in animals with experimental EOA and RPA not accompanied by disturbances in lipid and carbohydrate metabolism and significantly decreased the incidence of heart rhythm disturbances (Tables 1 and 2).

In animals with disturbances in lipid and carbohydrate metabolism, lidocaine exhibited no significant AAE. EOA were found in 40% rats and manifested in episodes of ventricular tachycardia and polytopic ventricular extrasystoles (Table 1). The development of RPA in animals with alloxan-cholesterol dyslipidemia was accompanied by not only significant decrease in AAE, but also manifestations of lidocaine cardiotoxicity, which was seen from more pronounced sinus bradycardia immediately after reperfusion (by 44% compared to animals with no metabolic disorders; and by 34% compared to rats with dyslipidemia without correction, $p<0.05$). Heart rhythm disorders were revealed in 80% animals. It should be emphasized that in 30% animals paroxysmal ventricular tachycardia was followed by ventricular fibrillation and death. Despite lidocaine injection, the total duration of RPA increased (30-600 sec, Table 2).

Pretreatment with LBK-149 had little effect on EOA and RPA in animals with disturbances in lipid and carbohydrate metabolism (Tables 1 and 2).

Taking into account the fact that combined administration of drugs can increase their effectiveness, we studied the effect of LBK-149 on AAE of lidocaine.

Additional treatment with LBK-149 increased AAE of lidocaine during experimental EOA accompanied by disturbances in lipid and carbohydrate metabolism, which manifested in a significant decrease in the incidence of heart rhythm disturbances (Table 1).

Resumption of coronary blood flow in animals with alloxan-cholesterol dyslipidemia receiving LBK-149 was also accompanied by potentiation of lidocaine AAE: sinus bradycardia was prevented, the incidence of RPA decreased, RPA were delayed (Table 2).

TABLE 1. AAE of Lidocaine on the Model of Early Occlusion Arrhythmias under Conditions of Dyslipidemia ($M\pm m$)

Group	n	HR, bpm			Frequency of ectopic contractions, min^{-1}	Arrhythmias		Conduction disturbances
		basal	after lidocaine administration	after occlusion		total	ventricular fibrillation	
Intact	12	375±30	—	260±53**	120±63	9	3	2
+lidocaine	10	355±23	306±11	280±22	220	1*	0	0
Dyslipidemia	10	340±72	—	253±30	30±14*	9	0	0
+lidocaine	10	396±38	342±32	300±42	96±38	4	0	0
+LBK-149	10	320±18	—	240±20	100±37	4	1	0
+lidocaine and LBK-149	7	375±24	271±21**	243±19**	41±4^{+}	2*^{o}	0	0

Note. Here and in Table 2: $p<0.05$: *compared to intact animals; **compared to the basal level; $^{+}$AAE of lidocaine in intact animals; ^{o}AAE of lidocaine against the background of dyslipidemia.

TABLE 2. AAE of Lidocaine during Myocardial Reperfusion under Conditions of Dyslipidemia (*M*±*m*)

Group	*n*	HR, bpm	Frequency of ectopic cardiac contractions, min^{-1}	Arrhythmias		Conduction disturbances	Start, sec	Duration, sec
				total	ventricular fibrillation			
Intact	9	247±46	90±36	9	0	2	13±5	300±86
+lidocaine	10	160±42	124±62	1*	1	1	4±1	30
Dyslipidemia	10	213±12	50±35	8	0	4	30±10	30±15*
+lidocaine	10	140±17*	120±44	8+	3	0	54±17+	30-600
+LBK-149	9	200±26	65; 40	2	0	2	45; 120	120; 250
+lidocaine and LBK-149	7	211±26+o	46±12	3*	0	0	280±87*+o	30-600

Our results indicate that additional administration of LBK-149 to animals with disturbances in the lipid and carbohydrate metabolism increases AAE and decreases cardiotoxicity of lidocaine on the model of EOA and RPA.

REFERENCES

1. O. V. Artem'eva and A. V. Zor'kina, *Ros. Kardiol. Zh.*, No. 5, 74-77 (2004).
2. L. A. Bokeriya, E. Z. Golukhova, M. G. Adamyan, *et al.*, *Kardiologiya*, No. 10, 17-24 (1998).
3. A. A. Kotlyarov and L. N. Sernov, *Ros. Kardiol. Zh.*, No. 5, 77-82 (2003).
4. M. S. Kushakovskii, *Cardiac Arrhythmias* [in Russian], St. Petersburg (1999).
5. V. Z. Lankin, A. K. Tikhaze, and Yu. N. Belenkov, *Kardiologiya*, No. 7, 48-61 (2000).
6. S. G. Priori, J. Barhanin, R. N. Hauer, *et al.*, *Circulation*, **99**, No. 4, 518-528 (1999).
7. M. Y. Yanse, *Clin. Cardiol.*, **1**, No. 14, 65-67 (1991).