Comparison of Antiarrhythmic Activities of Rihlocaine and Lidocaine

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 122, No. 11, pp. 517-520, November, 1996
Original article submitted February 12, 1996

In different models of arrhythmia, the local anesthetic rihlocaine (rinocaine) exhibits a higher (or comparable) antiarrhythmic activity and therapeutic spectrum than that of lidocaine. Antiarrhythmic activity of rihlocaine may be associated with its effect on sodium and, to a greater extent, on calcium channels.

Key Words: *rihlocaine; local anesthetics; antiarrhythmic drugs*

The local anesthetic rihlocaine (rinocaine, 1-allyl-2,5-dimethylpiperidole-4 benzoic ether hydrochloride) produces a pronounced effect upon infiltration and conduction anesthesia [9]. The antiarrhythmic properties of rihlocaine remain unstudied.

The aim of the present study was to compare antiarrhythmic activities (AAA) of rihlocaine and lidocaine.

MATERIALS AND METHODS

Experiments were carried out on 119 male Wistar rats (175-220 g), 24 outbred rabbits (2.8-3.6 kg), 91 cats (2.6-4.2 kg), and 18 dogs (14-22 kg) of both sexes.

The toxicity (mean lethal dose, LD_{50}) of the preparations was determined in rats after a single intravenous injection followed by a 48-h observation [8].

The effect on the ECG parameters (*R*, *RR*, *QT*, *P-Q*, *QRS*) was studied on cats narcotized with sodium nembutal (40 mg/kg, i.p.). The ECG was recorded in II standard lead.

The effects of the preparations on the following atrial [14] and ventricular arrhythmias was studied: early occlusion and reperfusion, including ventricular fibrillation [4] in cats and late heart rhythm disturbances (HRD) induced by myocardial infarction [12] in dogs. Antiarrhythmic activities of the drugs in atrial arrhythmia were assessed by biological titration [15], in ventricular arrhythmias by counting ectopic contractions as a percentage of heart contractions per minute recorded 24 h after occlusion of the descending branch of the left coronary artery.

In addition, AAA was studied using various HRD models: aconitine [6], epinephrine [10], and calcium chloride [1] (rats), barium chloride [13] (rabbits), and strophanthin [2] (cats). The AAA of rihlocaine and lidocaine were assessed by comparing their mean effective doses (ED_{50}) and antiarrhythmic indices (LD_{50}/ED_{50}) which allow one to assess the spectra of their therapeutic effects [3].

The effect of rihlocaine (10^{-4} M) on electromechanic coupling in the myocardium was studied on 12 atrial trabeculas of limnicous frogs (*Rana ridibunda*) [11].

The data were processed using statistical methods [3,7].

RESULTS

There was no significant difference between the toxicities of rihlocaine and lidocaine after intravenous administration (LD_{50} 28.2 and 28.0 mg/kg, respectively). Both drugs injected in isotoxic doses (10 and 15% of LD_{50}) induced no significant changes in ECG.

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0007-4888/96/0011-1099$15.00

TABLE 1. Effects of Isotoxic Doses of Rihlocaine and Lidocaine on Early Ventricular Arrhythmias in Cats

Drug	Dose, mg/kg	*n*	Early occlusion arrhythmias	Reperfusion arrhythmias	
				without arrhythmia	without fibrillation
Control		15	6	0	5
Rihlocaine	1.4	6	2	0	2
	2.8	6	3	3	4
	4.2	6	5*	5*	6*
Lidocaine	1.4				
	2.8	6	6*	4	5*
	4.6	7	7*	6*	7*

Note. *n*: number of animals, *$p<0.05$ compared with the control.

Under conditions of atrial arrhythmia rihlocaine exhibited pronounced AAA and in a dose of 2.5 mg/kg stopped atrial fibrillation, while lidocaine was ineffective.

In early ventricular HRD, rihlocaine (1.4 and 2.8 mg/kg, 5 and 10% of LD_{50}) exhibited no AAA and antifibrillatory activity. In a dose of 4.2 mg/kg (15% of LD_{50}) this drug prevented the early occlusion and reperfusion arrhythmias in 83% of animals and exhibited antifibrillatory activity in all cases. In a dose of 1.4 mg/kg (5% of LD_{50}) lidocaine exhibited no significant AAA or antifibrillatory activity. At 2.8 and 4.2 mg/kg (10 and 15% of LD_{50}) rihlocaine prevented the early occlusion arrhythmias in all animals and reperfusion arrhythmias in 85.7% of animals (the effect was statistically significant only for 4.2 mg/kg); ventricular fibrillation was not observed in 83.3 and 100% of animals, respectively (Table 1).

In late ventricular HRD, 4 mg/kg rihlocaine significantly reduced the number of ectopic contractions starting from 3 to 10 min postinjection. The maximum AAA was recorded on the 5th min of observation. The AAA of 4 mg/kg lidocaine was most pronounced on the 3rd min postinjection, persisting for 10 min. Both drugs produced no significant effect on heart rate, showing a tendency toward bradycardia (Table 2).

In the aconitine-induced arrhythmia rihlocaine exhibited no AAA, whereas lidocaine exerted an antiarrhythmic effect, ED_{50} being 7.5 mg/kg. Under conditions of calcium chloride-induced arrhythmia neither rihlocaine nor lidocaine exhibited any appreciable AAA. In epinephrine- and strophanthin-induced arrhythmias, rihlocaine was 2.0 and 2.1 times superior in AAA and 2.0 and 2.2 times in therapeutic activity. It should be noted that in strophanthin-induced arrhythmia, rihlocaine completely abolished HRD, whereas lidocaine stopped it only for 1.5-3 min. In barium chloride-induced arrhythmia, AAA and therapeutic dose range of rihlocaine and lidocaine were comparable (Table 3).

The higher AAA of rihlocaine than that of lidocaine in epinephrine- and strophanthin-induced ar-

TABLE 2. Effect of Rihlocaine (4 mg/kg) and Lidocaine (4 mg/kg) on Late Ventricular Arrythmias in Dogs (*M±m*, *n*=5)

Time, min	Parameter			
	heart rate, min^{-1}		ectopic contraction, %/min	
	rihlocaine	lidocaine	rihlocaine	lidocaine
Baseline	164.8±5.15	145.2±9.87	74.2±2.15	84.6±6.78
1	152.6±4.72	136.7±7.08	67.6±4.72	32.2±5.58*
3	146.2±5.36	128.5±5.36	30.0±1.29*	12.4±7.30*
5	148.5±5.58	134.3±5.79	28.3±0.86*	18.5±7.08*
10	156.3±4.72	141.7±4.94	36.0±1.50*	45.3±5.15*
15	160.8±6.00	144.2±7.30	58.7±1.72	67.4±6.01
20	159.2±4.29	146.5±4.72	70.5±5.58	75.6±5.36
30	160.8±5.36	142.8±6.44	74.4±5.15	88.4±6.22
40	158.4±6.44	143.6±7.94	72.8±4.29	82.4±6.22

Note. *$p<0.05$ compared with the baseline values.

TABLE 3. Antiarrhythmic Activities and Therapeutic Ranges of Rihlocaine and Lidocaine in Arrhythmias Induced with Epinephrine (Rats), Strophanthin (Cats), or Barium Chloride (Rabbits)

Drug	ED_{50}, mg/kg			LD_{50}, mg/kg	LD_{50}/ED_{50}		
	epinephrine	strophanthin	barium chloride		epinephrine	strophanthin	barium chloride
Rihlocaine	3.7 (2)	4.6 (2.1)	2.2 (0.9)	28.2 (1)	7.6	6.1	12.8
Lidocaine	7.4 (1)	9.8* (1)	2.0 (1)	28.0 (1)	3.8	2.8	14.0

Note. Values standardized to the effect of lidocaine taken as 1 are shown in parentheses. *Effect lasted 1.5-3 min.

rhythmias may be due to the effect of rihlocaine on slow calcium channels, since these two HRD models are specific for calcium channel blockers.

In experiments on isolated atrial trabeculas, rihlocaine lowered action potential by 4.9% and shortened its plateau by 14.4%, the slope being unchanged. The current threshold characterizing myocardial excitability decreased by 10%. Rihlocaine blocked Na^+, K^+, and Ca^{2+} transport through the corresponding channels. Perfusion with rihlocaine inhibited rapid Na^+ current by 36.4%, washout with normal saline did not restore Na^+ current, but the effect did not develop. Rihlocaine reduced the slow calcium inward current by 46.6%, temporal parameters of the calcium channel activation remained unchanged, whereas their conductivity dropped by 47%. The reversion potential, i.e., the potential corresponding to zero calcium current, decreased by 14 mV. Washout with normal saline partially restored the initial parameters of calcium current. Rihlocaine inhibited the instant potassium inward current by 39.3% at potentials below +50 mV. Hence, rihlocaine produces a pronounced membanotropic effect, decreases the amplitude of action potential and shortens its plateau, inhibits sodium, calcium, and potassium transmembrane currents, and exhibits the properties of sodium and, to a greater extent, calcium blocker and of potassium-sparing compound.

Thus, AAA and the therapeutic dose range of rihlocaine surpass (or are comparable to) those of lidocaine in various models of cardiac arrhythmia. The AAA of rihlocaine may be due to its action on sodium and, to a greater extent, on calcium channels. Rihlocaine can be used in clinical practice as an antiarrhythmic drug.

REFERENCES

1. G. N. Agafonova and V. N. Salyaev, *Farmakol. Toksikol.*, **41**, No. 5, 560-563 (1978).
2. E. M. Ammar and A. N. Kudrin, *Ibid.*, **32**, No. 5, 566-570 (1969).
3. M. L. Belen'kii, *Elements of Quantitative Evaluation of Pharmacological Effect* [in Russian], Leningrad (1963).
4. E. I. Gendenshtein, Ya. V. Kostin, N. N. Markelova, *et al.*, *Farmakol. Toksikol.*, **53**, No. 4, 28-30 (1990).
5. A. K. Grenader, *Antiarrhythmic Drugs, Ion Channel Blockers. Mechanisms and Structure* [in Russian], Pushchino (1987).
6. N. V. Kaverina and Z. P. Senova, *Methodical Recommendations on Experimental (Pharmacological) Study of Agents Submitted for Clinical Approbation as Drugs for Prevention and Treatment of Heart Rhythm Disturbances* [in Russian], Moscow (1981).
7. E. V. Montsevichute-Eringene, *Pat. Fiziol.*, No. 4, 71-78 (1964).
8. V. B. Prozorovskii and M. P. Prozorovskaya, *Farmakol. Toksikol.*, **43**, No. 6, 733-735 (1980).
9. A. A. Suleimenov and A. Zh. Nurmakov, *Eksp. Khir.*, No. 4, 56-58 (1974).
10. V. A. Shatalov and N. V. Dmitrieva, *Khim. Farm. Zh.*, No. 3, 322-326 (1986).
11. A. K. Filippov and I. Porotikov, *Gen. Physiol. Byophys.*, **2**, 95-106 (1983).
12. A. S. Harris, *Circulation*, **6**, 1318 (1950).
13. G. Y. Papp, L. Szekers, and T. Szmolenzky, *Acta Physiol. Acad. Sci. Hung.*, **32**, No. 4, 365-375 (1967).
14. A. Rosenblueth and G. Ramos, *Am. Heart J.*, **5**, 677 (1947).
15. M. Winbury and M. L. Hemmer, *Circ. Res.*, **111**, No. 5, 474 (1955).