NEW BIOMEDICAL TECHNOLOGIES

Effect of Biotechnological Cytochrome *c* on the Early Postocclusion and Reperfusion Arrhythmias

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Biotechnological cytochrome *c* showed a lower antiarrhythmic activity in cats with acute occlusion and reperfusion arrhythmias than trimecaine, verapamil, and quaternidine but a higher activity than anapriline. Under experimental conditions, cytochrome *c* potentiated the antiarrhythmic effect of trimecaine and quaternidine.

Key Words: *cytochrome c; occlusion and reperfusion arrhythmias; antiarrhythmic drugs*

Cytochrome *c* (Cc) is widely used for correction of tissue hypoxia in cardiology and other fields of clinical medicine [1,8,10]. Biotechnological methods for obtaining Cc developed at the Sintez-Belok Institute [4] cancel the limitations for its application. Biotechnological Cc, like its analog of animal origin, has a favorable effect on acute myocardial ischemia, improves cardiodynamics, and promotes a decrease in the size of necrotic zone [5,10]. Cc possesses an antiarrhythmic activity [2], but its place in combined therapy of heart rhythm disorders complicating the acute stage of myocardial infarction is still unclear.

We compared the antiarrhythmic activity of Cc with that of conventional antiarrhythmics of different classes and evaluated the effectiveness of their combinations in cats with occlusion and reperfusion arrhythmias.

MATERIALS AND METHODS

Experiments were carried out on 140 cats of both sexes weighing 2.5-3.5 kg. The animals were narcotized with sodium thiopental (40 mg/kg intraperitoneally). Acute occlusion and reperfusion arrhythmias were induced as described previously [11]. The duration of coronary artery occlusion was 30 min. The occurrence of occlusion and reperfusion arrhythmias (extrasystole and tachycardia) and ventricular fibrillations (VF) were evaluated. Antiarrhythmic activities of Cc, sodium channel blocker trimecaine, β-adrenoblocker anapriline (obsidan), polarizing potassium flow blocker quaternidine, and calcium antagonism verapamil (finoptin) were compared.

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RESULTS

In the control series, all animals developed early occlusion arrhythmias after high ligation of the coronary artery; 28% animals developed lethal VF. During coronary reperfusion the probability of VF markedly increased and reached 65% (Table 1).

Cytochrome *c* in doses of 5-20 mg/kg showed a pronounced antiarrhythmic activity, decreasing the probability of occlusion arrhythmias and reperfusion VF. Its antiarrhythmic effect was virtually dose-independent. Trimecaine (30 mg/kg) and verapamil (0.5-1.0 mg/kg) exerted stronger antiarrhythmic effects than Cc under the experimental conditions, the maximum dose of verapamil impaired cardiac conduction in all experiments. Quaternidine showed the highest antiarrhythmic activity; in a dose of 4 mg/kg it prevented early occlusion and reperfusion arrhythmias in all experiments without causing negative changes in the ECG. Anapriline was the least effective and in the studied doses displayed no antifibrillation activity.

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TABLE 1. Antiarrhythmic Activity of Cc Alone and in Combinations with Antiarrhythmics

Experimental conditions and dose, mg/kg		Number of animals					
		experiment	occlusion		experiment	reperfusion	
			arrhythmia	VF		arrhythmia	VF
Control	—	28	28 (100)	8 (28)	20	20 (100)	13 (65)
Cc,	20	7	3 (43)*	0	7	6 (86)	1 (14)*
	10	6	4 (67)*	0	6	6 (100)	1 (17)*
	5	10	5 (50)*	1 (10)	9	4 (44)*	3 (33)
Trimecaine,	30	7	1 (14)*	0	7	3 (43)*	0*
	10	6	5 (83)	0	6	6 (100)	3 (50)
Anapriline,	2.5	6	4 (67)*	0	6	6 (100)	3 (50)
	1	6	2 (33)*	0	6	5 (83)	3 (50)
	0.5	5	4 (80)	0	5	5 (100)	2 (40)
Quaternidine,	4	6	0*	0	6	0*	0*
	2	12	3 (25)*	0	12	4 (33)*	0*
	0.5	6	3 (50)*	1 (17)	6	6 (100)	2 (33)
Verapamil,	1	3	1 (33)*	0	3	0*	0*
	0.5	8	2 (25)*	0	8	3 (38)*	1 (13)*
	0.3	5	4 (80)	0	5	5 (100)	3 (60)
Cc, 5+trimecaine,	10	6	0*	0	6	6 (100)	1 (17)*
Cc, 5+anapriline,	1	7	2 (29)*	0	7	7 (100)	2 (29)
Cc, 5+quaternidine,	0.5	5	3 (60)*	0	5	3 (60)*	2 (40)
Cc, 5+verapamil,	0.3	6	4 (67)*	0	6	5 (83)	3 (50)

Note. *$p<0.05$ *vs.* the control, the percentage is given in parentheses.

We then evaluated the effect of Cc on antiarrhythmic activities of trimecaine, anapriline, quaternidine, and verapamil. In accordance with the previously described method [3,6,7], the drugs were combined in doses in which they did not exert the maximum antiarrhythmic and antifibrillation effects.

Cytochrome *c* did not increase the efficacy of anapriline and verapamil in occlusion and reperfusion arrhythmias. In experiments with the Cc-quaternidine combination, only 3 out of 5 animals developed reperfusion arrhythmias ($p<0.05$), while in monotherapy with both drugs arrhythmias occurred in 100% cases; this can be regarded as a manifestation of synergistic effect of the drugs.

The combination of Cc with trimecaine was the most effective. Monotherapy with Cc and trimecaine in the dose subsequently used in the combination led to development of arrhythmias in 50 and 83% cases, respectively, while after combined therapy, none of the experimental animals developed occlusion arrhythmias. Moreover, in contrast to the monotherapy, combined therapy significantly decreased the probability of reperfusion VF, but did not prevent other types of reperfusion arrhythmias.

The efficacy of the above-mentioned combinations may be explained by the ability of their components to affect various links in the pathogenesis of cardiac arrhythmias. Conventional antiarrhythmics block transmembrane ionic currents in cardiomyocytes [9, 12], and Cc interferes into pathogenetically primary components of arrhythmogenesis, specifically, corrects the energy metabolism in ischemic myocardium [5,10].

Thus, Cc exerts antiarrhythmic effect under conditions of experimental acute myocardial infarction and the reperfusion syndrome. Although its activity is lower than that of trimecaine, quaternidine, and verapamil, its antifibrillation effects are sufficiently high. Cytochrome *c* can be used in combinations with the polarizing potassium blocker quaternidine and the sodium flow blocker trimecaine.

REFERENCES

1. I. G. Andrianova, N. D. Sidorova, and E. A. Selivanova, in: *Cytochrome C and Its Clinical Application* [in Russian], Leningrad (1990), pp. 30-37.
2. V. P. Balashov, L. A. Balykova, Ya. V. Kostin, and L. N. Sernov, *Eksp. Klin. Farmakol.*, No. 2, 17-19 (1996).

3. V. P. Balashov, Ya. V. Kostin, D. G. Sedova, *et al.*, *Byull. Eksp. Biol. Med.*, **115,** No. 6, 629-630 (1993).
4. V. V. Beregovykh, E. R. Davidov, V. I. Kozlov, *et al.*, *Khim.-Farm. Zh.*, No. 10, 14-22 (1990).
5. V. V. Gatsura, *Drug Correction of Energy Metabolism in Ischemic Myocardium* [in Russian], Moscow (1993).
6. E. I. Gendenshtein, Ya. V. Kostin, V. P. Balashov, *et al.*, *Farmakol. Toksikol.*, No. 4, 28-30 (1990).
7. E. I. Gendenshtein, Ya. V. Kostin, V. P. Balashov, and V. E. Oleinikov, *Byull. Eksp. Biol., Med.*, **111,** No. 6, 623-625 (1991).
8. V. A. Zinchenko and N. D. Sidorova, *Klin. Med.*, No. 9, 49-51 (1985).
9. N. A. Mazur and A. Abdalla, *Drug Therapy of Arrhythmias* [in Russian], Moscow (1995).
10. L. N. Sernov, V. V. Beregovykh, E. R. Davidov, and V. V. Gatsura, *Biotechnological Cytochrome C (Chemistry. Pharmacology)* [in Russian], Moscow (1997).
11. B. G. Storozhuk, *Farmakol. Toksikol.*, No. 3, 47-49 (1985).
12. E. M. Vaughan-Williams, *J. Clin. Pharmacol.*, **24,** 129-147 (1984).