

Effect of Befol on the Electric Threshold of Ventricular Fibrillation

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Befol (20 mg/kg) rises electric threshold of ventricular fibrillation in cats. This effect is most pronounced in ischemized myocardium. It is shown that not only tricyclic but also monocyclic antidepressants exhibit antifibrillatory activity.

Key Words: *befol; ventricular fibrillation; ischemia, treatment*

The antidepressant befol, 4-chlorine-N-(3-morpholinopropyl)-benzamide hydrochloride, is a reversible inhibitor of monoamine oxidase (type A by serotonin substrate) synthesized at the Institute of Pharmacology (Russian Academy of Medical Sciences) [1,4]. Clinical trials showed that this drug possesses both antidepressant and antiarrhythmic activities [3,6].

Therefore, it was interesting to assess the antifibrillatory activity (AFA) of befol, which is a monocyclic antidepressant, in animal experiments, bearing in mind the finding that some tricyclic antidepressants (metapramine, imipramine, and momephenzin) exhibit AFA in acute regional myocardial ischemia (ARMI) [8-10,12].

MATERIALS AND METHODS

Experiments were performed on anesthetized (sodium pentobarbital, 40 mg/kg, intravenously) cats (body weight 2.3-3.0 kg) of both sexes. Catheters were inserted in the right femoral vein for befol infusion and in the left femoral artery for measuring arterial pressure with an Elema-Simens electromanometer. Silver bipolar electrodes were sutured to the right ventricle of the heart after thoraco- and pericardiotomy. After a 10-min stabilization period, electric

threshold of ventricular fibrillation (ETVF) was determined by scanning the electrically vulnerable period of cardiac cycle (ascending portion of *T* wave) with a series of 20 rectangular direct current pulses of increasing intensity (pulse duration 4 msec, frequency 50 pulses/sec) until the appearance of ventricular fibrillation. Electrocardiogram (lead II) was recorded with an EKChT-02 electrocardiograph with a simultaneous record in an Attack-359 analyzer (Nihon Kohden). Direct electric countershock was delivered from a DI-3 apparatus. Acute regional myocardial ischemia was produced by occlusion of the descending branch of the left coronary artery between its upper and middle thirds. Befol was slowly infused using a Syringer Pump 355 (Sage Instruments). Three series of experiments (5 cats in each) were performed. In the first series, the effect of befol (5, 10, 15, and 20 mg/kg) on ETVF was studied in intact cats. In the second series, the effect of ARMI on ETVF was examined. In the third series, the effect of befol (20 mg/kg) on ETVF was assessed in cats with ARMI. The results were statistically processed using conventional methods [5].

RESULTS

At 5 and 10 mg/kg befol had no appreciable effect of ETVF (Table 1). A tendency toward an increase in ETVF was observed at 15 mg/kg, and a statistically significant rise of ETVF by 2.2 times was recorded

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TABLE 1. Effect of Befol on Ventricular Fibrillation in Anesthetized Cats with Intact Myocardium

Experiment No.	ETVF (mA) at befol dose, mg/kg							
	5		10		15		20	
	control	experiment	control	experiment	control	experiment	control	experiment
1	3.25	3.00	1.75	2.00	3.75	4.25	4.00	9.00
2	2.50	2.50	2.75	2.75	1.25	2.75	2.25	5.20
3	4.00	4.00	4.25	4.00	1.50	1.75	1.75	3.15
4	2.75	2.75	3.50	3.75	1.25	2.00	3.00	6.00
5	1.50	1.50	2.25	2.50	2.75	3.25	1.00	2.75
<i>M±m</i>	2.80±0.54	2.75±0.54	2.90±0.54	3.00±0.43	2.10±0.54	2.80±0.54	2.40±0.64	5.22±0.84*

Note. * $p < 0.05$ compared with control.

at 20 mg/kg. It should be noted that in befol-treated cats ventricular fibrillation was induced by stronger currents, cardiac rhythm spontaneously normalized in 3 out of 5 cats, and fibrillation lasted less than 30 sec. The antifibrillatory effect of befol was observed for at least 2 h.

By the 30th min of ARMI, ETVF decreased by 51.3% compared with that before occlusion of the left coronary artery (Table 2). In some cats, not only ETVF decreased but also the amplitude of defibrilating discharge was higher. The ETVF did not change significantly for 2 h from the moment of occlusion. The results obtained in this experimental series were similar to the published data [11].

After administration of 20 mg/kg befol between the 25th and 30th min of ARMI, we failed to induce irreversible ventricular fibrillation even by applying stimulating pulses of 10-fold higher intensity. A short (<30 sec) fibrillation was observed upon stimulation with 2- to 4-fold higher pulses. Spontaneous normalization of cardiac rhythm was observed in all animals. The effect of befol lasted at least 2 h.

Thus, befol exhibits pronounced AFA that reaches the maximum in ARMI.

So far, the mechanism underlying AFA of befol are unknown. It can be suggested that this activity is associated with the ability of befol to modulate $\text{Na}^+/\text{Ca}^{2+}$ exchange in cardiomyocytes [7].

The possibility cannot be ruled out that the inhibitory effect of befol on the sympathetic influences on the heart contributes to antifibrillatory activity [7], which is particularly important in ischemia. There is indirect evidence that befol has β -adrenoblocking activity [3]. Central mechanisms may also play a role in realization of AFA, since the preparation prevents arrhythmias of the central genesis induced by injection of aconitine and barium chloride in the fourth ventricle of the brain [7].

Our results indicate that not only tricyclic but also monocyclic antidepressants exhibit antifibrillatory activity, and the mechanisms of this activity are much more complicated than had been suspected.

TABLE 2. Effect of Befol (20 mg/kg) on Ventricular Fibrillation in Anesthetized Cats with Myocardial Ischemia

Experiment No.	ETVF, mA						
	control			experiment			
	background	ischemia, min		background	ischemia+befol, min		
		30	120		20-25*	45	120
1	1.50	0.40	0.50	4.00	3.25	>10	>20
2	2.75	1.25	1.25	3.25	1.20	>10	>7
3	4.25	2.75	2.50	2.50	1.20	>10	>10
4	3.50	1.30	1.30	4.00	2.25	>10	>8
5	1.25	0.75	1.00	0.75	0.50	>10	>7
<i>M±m</i>	2.65±0.64	1.29±0.43*	1.31±0.43*	2.90±0.71	1.68±0.60*		

Note. *Time after befol was administered. * $p < 0.05$ compared with background values.

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