Comparison of Antiarrhythmic Activities of Befol, Lidocaine, and Bonnecor

P. A. Galenko-Yaroshevskii, A. I. Khankoeva, A. V. Uvarov, A. Yu. Reznikov, D. S. Galygo, and V. V. Bartashevich

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 122, No. 12, pp. 665-668, December, 1996
Original article submitted January 19, 1996

The antiarrhythmic activity of befol (an isotoxic dose) is higher than (or comparable to) that of lidocaine and bonnecor in atrial and ventricular arrhythmias induced by acute ischemia, reperfusion, myocardial infarction, or ouabain treatment. In epinephrine-induced arrhythmia, befol is inferior to these drugs (except lidocaine) in activity and range of therapeutic action.

Key Words: *befol; lidocaine; bonnecor; arrhythmias; treatment*

Befol [4-chloro-N-(3-morpholinopropyl)-benzamide hydrochloride], a Russian-manufactured antidepressant, is a reversible monoamine oxidase inhibitor selectively inhibiting serotonin deamination [3].

This drug is effective against cardiac rhythm disturbances (CRD) of ischemic and nonischemic origin [10].

The aim of the present study was to compare the antiarrhythmic activities (AAA) of befol, lidocaine, and bonnecor in experiments on animals with various CRD.

MATERIALS AND METHODS

Experiments were performed on 205 male Wistar rats (0.170-0.240 kg), 9 rabbits (2.4-3.6 kg), 107 cats (2.8-4.4 kg), and 25 dogs (7-25 kg).

Acute toxicity (mean lethal dose, LD_{50}) of befol, lidocaine, and bonnecor was determined in experiments on rats (intravenous injections).

The antiarrhythmic activities of the drugs were studied in atrial [16], ventricular, and atrioventricular arrhythmias. The following ventricular CRD were modeled: early occlusion and reperfusion arrhythmias, including ventricular fibrillation [4] and late CRD induced by myocardial infarction [13] in cats, and dogs; epinephrine- [12] and calcium chloride-induced [1] arrhythmias in rats; barium chloride-induced arrhythmia [14] in rabbits and ouabain-induced arrhythmia in cats (0.05 mg/kg with successive injection of 0.01 mg/kg each 10 min until extrasystole and ventricular tachycardia appeared). Atrioventricular arrhythmia was induced by aconitine [5] in rats. Antiarrhythmic activity was evaluated by biological titration [17] in atrial arrhythmias, by the difference in CRD incidence in experimental and control animals with ventricular CRD induced by acute ischemia and reperfusion, and by the percentage of ectopic ventricular contractions recorded 24 h after occlusion of descending branch of the left coronary artery in CRD induced by myocardial infarction. The AAAs of the drugs were compared by the isotoxic dose. In chemically-induced CRD, AAA was assessed by the mean effective dose (ED_{50}), mean lethal dose (LD_{50}), and antiarrhythmic index (LD_{50}/ED_{50}), which characterizes the range of therapeutic action [2]. Befol, lidocaine, and bonnecor were injected intravenously in ascending doses.

The data were processed statistically by the methods described previously [2,8].

RESULTS

Befol exhibited pronounced AAA activity in atrial CRD. Its dose sufficient to stop atrial flutter did not differ significantly from that of bonnecor (2.7±0.96 *vs.* 2.3±0.45 mg/kg). It should be noted that in 3

Department of Pharmacology, Kuban State Medical Academy, Krasnodar

0007-4888/96/0012-1225$15.00

TABLE 1. Effectiveness of Befol, Lidocaine, and Bonnecor in Early Occlusion and Reperfusion Arrhythmias in Cats

Drug	Dose, mg/kg	*n*	Early occlusion arrhythmias (number of cats without arrhythmias)	Reperfusion arrhythmia (number of cats)	
				without arrhythmia	without fibrillation
Control		15	6	0	5
Befol	11.7	6	3	1	4
	23.4	7	6*	6*	7*
	35.0	6	6*	6*	6*
Lidocaine	1.4	11	4	5	6
	2.8	6	6*	4	5*
	4.2	7	7*	6*	7*
Bonnecor	0.6	6	1	2	2
	1.2	6	5*	5*	5*
	1.8	7	6*	6*	7*

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

out of 5 cases bonnecor induced conduction disturbances of various intensities. Lidocaine was not tested in atrial CRD, since in therapeutic doses it is ineffective against these arrhythmias [6].

As Table 1 shows, occlusion arrhythmia did not develop in 40% of the control cats, while reperfusion arrhythmia occurred in all cases and in 67% cats it turned into ventricular fibrillation. Befol (11.7 mg/kg, 5% LD_{50}) did not prevent these CRD. Higher doses of befol (23.4 and 35.0 mg/kg, 10 and 15% LD_{50}, respectively) prevented the early occlusion and reperfusion arrhythmias in 85.7% (23.4 mg/kg) or 100% (35.0 mg/kg) of the cats; none of the animals developed ventricular fibrillation. At 1.4 mg/kg (5% LD_{50}) lidocaine exhibited no appreciable AAA and antifibrillatory activity. At 2.8 and 4.2 mg/kg (10 and 15% LD_{50}) it prevented the early occlusion arrhythmias in 100%, reperfusion arrhythmia in 67% (statistically insignificant) and 85.7%, and ventricular fibrillation in 83.3 and 100% of cats, respectively. In a dose of 0.6 mg/kg (5% LD_{50}) bonnecor showed no significant antiarrhythmic and antifibrillatory activities. After administration in higher doses (1.2 and 1.8 mg/kg, 10 and 15% LD_{50}), it prevented occlusion and reperfusion arrhythmia in 83.3 and 85.7% and ventricular fibrillation in 83.3 and 100% of experimental animals, respectively.

In a dose equal to 15% LD_{50} befol, lidocaine, and bonnecor were effective against ventricular CRD developing at the late stages of myocardial infarction (Table 2). For instance, in a dose of 35 mg/kg befol significantly decreased the number of ventricular ectopic beats from the 1st till the 120th min postinjection, and eliminated this CRD for 10 min. The antiarrhythmic effect of lidocaine (4.2 mg/kg) was ob-

TABLE 2. Effects of Befol (35 mg/kg), Lidocaine (4.2 mg/kg), and Bonnecor (1.8 mg/kg) on Ventricular Ectopic Beats in Dogs with Experimental Myocardial Infarction (*M±m*, *n*=5)

Time, min	Heart rate, min^{-1}			Ventricular ectopic beats, %/min		
	befol	lidocaine	bonnecor	befol	lidocaine	bonnecor
Background	168.0±8.6	162.0±5.2	152.0±3.0	74.0±7.3	65.0±4.3	78.0±6.4
1	162.0±5.4	158.0±4.5	144.0±7.5	0	6.0±1.3*	56.0±7.9
3	156.0±6.9	154.0±6.7	130.0±3.6*	0	18.0±2.1*	0
5	158.0±4.9	156.0±5.8	128.0±4.1*	0	24.0±1.5*	0
10	157.0±7.7	155.0±6.4	132.0±3.9*	0	52.0±4.7	25.0±2.4*
20	159.0±6.0	159.0±5.6	145.0±8.2	3.8±0.6*	56.0±4.5	66.0±7.9
30	164.0±7.3	157.0±6.0	148.0±7.7	7.0±1.3*	58.0±4.3	68.0±6.7
60	162.0±5.6	163.0±3.9	156.0±4.7	18.0±1.5*	64.0±4.9	72.0±5.2
120	166.0±6.4	157.0±7.5	152.0±5.1	32.0±2.8*	62.0±5.2	76.0±4.7
150	162.0±5.8	160.0±4.3	149.0±4.7	68.0±4.5	56.0±4.3	69.0±6.4

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

TABLE 3. Antiarrhythmic Activities of Befol, Lidocaine, and Bonnecor in Epinephrine-Induced Arrhythmia in Rats

Drug	AAA		Acute toxicity		LD_{50}/ED_{50}
	ED_{50}, mg/kg	relative AAA	LD_{50}, mg/kg	relative acute toxicity	
Befol	34.7 (30)	0.02	233.8 (35)	0.05	6.7
Lidocaine	7.6 (30)	0.09	28.0 (25)	0.43	3.7
Bonnecor	0.7 (25)	1	12.0 (30)	1	17.1

Note. Number of animals is given in parentheses.

served from the 1st till the 15th min postinjection and reached the maximum within the 1st min. Bonnecor (1.8 mg/kg) produced a significant antiarrhythmic effect on the 2nd-3rd min postinjection. There were no ventricular ectopic beats from the 3rd till the 5th min; the effect lasted 10 min. The heart rate slightly dropped during the first 10-20 min after injection of befol and lidocaine, and significantly decreased from the 3rd till the 10th min after injection of bonnecor.

Befol (11.7 mg/kg, 5% LD_{50}) prevented the ouabain-induced arrhythmia in 2 out of 5 cats (40%), the duration of effect being 7 and 12 min; 60% of the animals died. Injection of 23.4 mg/kg befol (10% LD_{50}) prevented CRD in 100% of cats, AAA being observed manifest against the background of ouabain-induced atrioventricular blockade (in 60% of cats). Lidocaine (2.8 and 4.2 mg/kg, 10 and 15% LD_{50}) exhibited AAA in 40 and 60% of cats (2 groups, n=5), the effect occurring within 12-15 min. It should be noted that in the first group 60% of cats died, whereas in the second group 40% of cats survived. Bonnecor (1.2 and 1.8 mg/kg, 10 and 15% LD_{50}) stopped CRD in 20 and 40% cats, respectively (2 groups, each consisting of 5 animals), the effect lasting 15-20 min; 60 and 40% of animals died. It should be noted that bonnecor (1.8 mg/kg) induced tachycardia in 2 cats. In doses of 10, 20, and 40 mg/kg befol exhibited a low AAA in calcium chloride-, barium chloride-, and aconitine-induced arrhythmias.

In epinephrine-induced arrhythmia, befol was less effective than lidocaine and bonnecor. The AAA of bonnecor was 4.6- and 49.6-fold lower than that of lidocaine and bonnecor, respectively, while its range of therapeutic action was 1.8-fold broader than that of lidocaine, but 2.5-fold narrower than that of bonnecor (Table 3).

Thus, AAA of befol in atrial and ventricular CRD induced by acute ischemia, reperfusion, myocardial infarction, and ouabain is higher than (or comparable to) that of lidocaine and bonnecor. It is noteworthy that the maximum AAA of befol was observed in atrial and ventricular arrhythmias caused by myocardial infarction. In epinephrine-induced arrhythmia, the AAA of befol was lower than that of the reference drugs and its range of therapeutic action was narrower (except that of lidocaine). Befol showed no AAA in CRD induced by aconitine, calcium chloride, and barium chloride.

The AAA of befol may be associated with its effect on the central serotoninergic stress-limiting systems [9], which compensates for electrical instability of the heart [7], and with its ability to modulate transmembrane ion currents in cardiomyocytes [11]. The possibility that the antiarrhythmic effect of befol is mediated by myocardial receptors, which may serve as the target for antiarrhythmic agents [15], cannot be ruled out.

REFERENCES

1. G. N. Agafonova and V. N. Salyaev, *Farmakol. Toksikol.*, **41**, No. 5, 560-563 (1978).
2. M. L. Belen'kii, *Elements of Quantitative Evaluation of Pharmacological Effect* [in Russian], Leningrad (1963).
3. E. M. Gankina, M. F. Mineeva, D. Yu. Rusakov, *et al.*, in: *Befol: An Original Antidepressant* [in Russian], Moscow (1990), pp. 69-87.
4. E. I. Gendenshtein, Ya. V. Kostin, N. N. Markelova, *et al.*, *Farmakol. Toksikol.*, **53**, No. 4, 28-30 (1990).
5. N. V. Kaverina and Z. P. Senova, *Methodological 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).
6. M. S. Kushakovskii, *Cardiac Arrhythmias* [in Russian], St. Petersburg (1992).
7. F. Z. Meerson and M. G. Pshennikova, *Adaptation to Stress Situations and Physical Exercises* [in Russian], Moscow (1988).
8. V. B. Prozorovskii, *Farmakol. Toksikol.*, **25**, No. 1, 115-119 (1962).
9. V. V. Skibitskii, "Pharmacological activation of stress-limiting system in the therapy of cardiac rhythm disturbances" [in Russian], Author's Synopsis of Doct. Med. Sci. Dissertation, Moscow (1993).
10. V. V. Skibitskii and S. G. Kanorskii, *Eksp. Klin. Farmakol.*, **56**, No. 5, 23-27 (1993).
11. A. I. Khankoeva, "Approaches to reduction of cardiotoxicity of antiarrhythmic drugs in ischemic myocardium" [in Russian], Author's Synopsis of Dissertation, Rostov-on-Don (1995).
12. V. A. Shatalov and N. V. Dmitrieva, *Khim.-Farm. Zh.*, No. 3, 322-326 (1986).
13. A. S. Harris, *Circulation*, **6**, 1318 (1950).
14. G. Y. Papp, L. Szekers, T. Szmolenzky, *Acta Physiol. Acad. Sci. Hung.*, **32**, No. 4, 365-375 (1967).
15. M. R. Rosen, *Ibid.*, **84**, 1831-1856 (1991).
16. A. Rosenblueth and G. Ramos, *Am. Heart J.*, **5**, 677 (1947).
17. M. Winbury and M. L. Hemmer, *Circ. Res.*, **111**, No. 5, 474 (1955).