Effect of Befol and Sufan on Neurogenic Atrial Fibrillation

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Antiarrhythmic activity of befol in neurogenic atrial fibrillation is due to its cardiotropic and cholinolytic effects and coincides with the dynamics of the tonic component of vagal chronotropic influence. Unlike befol, sufan has no effect on the duration of atrial fibrillation despite a reduction of synchronizing component of the vagal chronotropic influence. Tonic component remains unchanged, which is probably responsible for the absence of antiarrhythmic activity of sufan.

Key Words: *vagus nerve; neurogenic atrial fibrillation; befol; sufan; antiarrhythmic effect; vagolytic effect; cardiotropic effect*

The antidepressant befol (4-chlor-N-(3-morpholinopropyl)-benzamine hydrochloride, monoamine oxidase type A inhibitor, serotonin antagonist) [1,2, 8,10] and the nonglycoside cardiotonic sufan (N-succine-dl-tryptophan dipotassium salt) [9] diminish cardiotoxic effects of bonnecor, propranolol, verapamil, and other antiarrhythmic drugs [15]. Befol and sufan also possess intrinsic antiarrhythmic activity in various models of cardiac rhythm disturbances (CRD) and potantiate the effect of antiarrhythmic drugs.

For instance, befol has an antiarrhythmic effect in atrial arrhythmia induced by damage to the sinus node, early and delayed occlusion and reperfusion ventricular CRD induced by myocardial ischemia and elevates ventricular fibrillation threshold. Befol is superior to quinidine, ethmozine, and bonnecor in antiarrhythmic activity (in isotoxic doses) [3,15]. Antiarrhythmic effects of verapamil and bonnecor in delayed ventricular CRD can be potentiated by befol+ verapamil and by befol+bonnecor [15]. Befol elicits antiarrhythmic effect in central CRD induced by injection of aconitine, barium chloride or ouabaine into the fourth brain ventricle [15]. The antiarrhythmic activity of befol is associated with modulation of Na/Ca^{2+} exchange in cardiomyocytes [13,16], antianginal properties [15], and activation of stress-limiting systems due to accumulation of serotonin in the central nervous system [14].

Sufan can prevent and stop reperfusion-, strophanthin-, and barium chloride-induced arrhythmias. Its antiarrhythmic effect is comparable to that of lidocaine. Sufan potentiates antifibrillatory effect of lidocaine in reperfusion arrhythmia [4]. Antiarrhythmic activity of sufan is mediated through modulaton of Ca^{2+} exchange in cardiomyocytes [5,6].

The aim of the present study was to evaluate antifibrillatory activity of befol and sufan under conditions of neurogenic atrial fibrillation (NAF), the most adequate model of natural atrial CRD.

MATERIALS AND METHODS

Experiments were carried out on 16 cats weighing 2.5-4.5 kg. The animals were narcotized with Chloralose-Nembutal and artificially ventilated.

The method was described in details elsewhere [7, 12]. Befol (n=8) and sufan (n=8) were injected intravenously in doses of 20 and 40 mg/kg, respectively.

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The data were processed statistically [3], the mean and its deviation for each parameter and significance of differences were determined.

RESULTS

Experimental data on the effect of befol and sufan on cardiac function and the duration of CRD are summarized in Tables 1 and 2.

Befol reduced the duration of atrial fibrillation as soon as 5 min postinjection and even completely arrested it in 3 experiments; 30 min postinjection the antifibrillatory effect of befol weakened and by the 60th and 120th min parameters of arrhythmia did not differ from the control.

The antifibrillatory effect of befol coincided with its vagolytic effect, which manifests itself in a reduction of tonic and synchronizing components of the chronotropic vagal influence and peaked 5 min postinjection. Thirty minutes postinjection, we observed a gradual recovery of suppressed vagal influence, while after 60 and 120 min tonic component of vagal chronotropic influence and the duration of fibrillation practically did not differ from the initial levels.

Suppression of the synchronizing component persisted to the end of the experiment (120 min).

TABLE 1. Effect of Befol on Cardiac Function and Duration of Atrial Fibrillation in Cats Induced by Stimulation of Vagus Nerve (VN) (*M±m*)

Parameter	Initial value	Time postinjection, min			
		5	30	60	120
Baseline P-P interval, msec	374±5 (100)	420±10 (112)*	399±10 (107)*	378±9 (101)	375±6 (100)
Excitation threshold of vagus nerve, V	0.35±0.04 (100)	0.57±0.08 (163)*	0.44±0.04 (126)	0.39±0.02 (111)	0.38±0.03 (109)
Components of vagal chronotropic effect, msec:					
synchronizing	244±28 (100)	24±4 (10)*	94±24 (39)*	161±28 (66)*	169±35 (69)*
tonic	82±14 (100)	11±2 (13)*	44±8 (54)*	72±14 (88)	70±13 (85)
Atrial excitation threshold, V	0.38±0.04 (100)	0.51±0.04 (134)*	0.46±0.03 (121)	0.42±0.04 (111)	0.41±0.03 (108)
Effective refractory period, msec	146±7 (100)	174±9 (119)*	166±10 (114)*	158±8 (108)	152±7 (104)
Sinoatrial conductance, msec	19±1 (100)	17±1 (89)*	19±1 (100)	20±1 (105)	19±1 (100)
P-Q interval, msec	74±3 (100)	76±3 (103)	75±3 (101)	74±3 (100)	73±3 (99)
Duration of atrial fibrillation, sec	201±50 (100)	12±6 (6)*	47±14 (23)*	118±35 (59)	138±33 (69)

Note. Here and in Table 2: percentage is shown in parentheses, *$p<0.05$ compared with the initial values.

TABLE 2. Effect of Sufan on Cardiac Function and Duration of Atrial Fibrillation in Cats Induced by Stimulation of the Vagus Nerve (VN) (*M±m*)

Parameter	Initial value	Time postinjection, min			
		5	30	60	120
Baseline P-P interval, msec	378±6 (100)	379±6 (100)	378±6 (100)	380±8 (100)	380±6 (100)
Excitation threshold of vagus nerve, V 0.48±0.03	0.44±0.03 (100)	0.48±0.05 (109) (109)	0.51±0.02 (116)	0.48±0.03	(109)
Components of vagal chronotropic effect, msec:					
synchronizing	322±37 (100)	225±29 (70)*	219±28 (68)*	235±41 (73)*	219±41 (68)*
tonic	100±14 (100)	82±13 (82)	89±14 (89)	85±14 (85)	85±13 (85)
Atrial excitation threshold, V	0.43±0.09 (100)	0.40±0.07 (93)*	0.43±0.08 (100)	0.40±0.08 (93)	0.41±0.09 (95)
Effective refractory period, msec	139±3 (100)	141±5 (101)	138±5 (99)	144±3 (103)	138±4 (99)
Sinoatrial conductance, msec	21±1 (100)	21±1 (100)	21±1 (100)	21±1 (100)	22±1 (105)
P-Q interval, msec	76±4 (100)	74±4 (97)	76±4 (100)	75±4 (99)	74±4 (97)
Duration of atrial fibrillation, sec	284±84 (100)	336±101 (118)	316±59 (111)	280±49 (99)	262±52 (92)

This suggests that antiarrhythmic effect is related only to the dynamics of tonic component of vagal chronotropic influence.

Cardiotropic effect of befol manifests itself in impaired automatism, elevated threshold of myocardial excitability, and prolonged effective atrial refractory period. Befol had no effect on conductance as evidenced by unaltered *P-Q* interval and even slightly accelerated sinoatrial conductance at the initial stage of the experiment.

Thus, antifibrillatory activity of befol results from its cardiotropic and cholinolytic effects preventing early repolarization of cardiomyocyte membrane.

Unlike befol, sufan exhibited no antiarrhythmic activity in NAF. Moreover, in 4 experiments sufan prolonged fibrillation.

Experimental data attest to negligible cholinolytic effect of sufan, which manifest itself in suppression of the synchronizing component of vagal chronotropic influence, the tonic component being unaffected. The latter presumably explains the absence of antifibrillatory effect of sufan, since the nature and duration of NAF is determined by tonic influence of the vagus nerve. Sufan also had no effect on excitatory threshold of the vagus nerve.

A positive cardiotropic effect of sufan consisted in a decrease of myocardial excitability threshold against the background of unchanged effective refractory period. The latter is presumably responsibly for prolongation of NAF in some experiments, but this phenomenon did not change the average dynamics of this parameters.

REFERENCES

1. A. V. Val'dman, M. M. Kozlovskaya, and A. P. Muzychenko, *Express-Information. Novye Lekarstvennye Preparaty*, No. 11, 1-11 (1988).
2. T. A. Voronina, L. N. Nerobkova, N. V. Markina, *et al.*, in: *Befol, a New Original Russian-Manufactured Antidepressant* [in Russian], Moscow (1990), pp. 49-56.
3. P. A. Galenko-Yaroshevskii, S. A. Kryzhanovskii, M. B. Vititnova, and A. I. Khankoeva, *Byull. Eksp. Biol. Med.*, **123**, No. 3, 305-307 (1997).
4. P. A. Galenko-Yaroshevskii, A. V. Uvarov, D. S. Galygo, *et al., Ibid*, No. 5, pp. 545-547.
5. P. A. Galenko-Yaroshevskii, A. I.Khankoeva, and A. S. Dukhanin, *Ibid,*, **122**, No. 7, 57-59 (1996).
6. P. A. Galenko-Yaroshevskii, A. I.Khankoeva, A. S. Dukhanin, and D. S. Galygo, *Ibid.*, No. 8, pp. 170-172.
7. P. A. Galenko-Yaroshevskii, I. L. Cherednik, V. V. Bartashevich, *et al., Ibid.*, **124**, No. 7, 81-85 (1997).
8. E. M. Gankina, M. F. Mineeva, D. Yu. Rusakov, *et al.*, in: *Befol, a New Original Russian-Manufactured Antidepressant* [in Russian], Moscow (1990), pp. 69-87.
9. A. I. Grinevich, I. S. Chekman, P. A. Galenko-Yaroshevskii, *et al., Dokl. Akad. Nauk. Ukraine*, No. 5, 169-173 (1994).
10. M. M. Kozlovskaya, A. P. Muzychenko, V. V. Kushnarev, *et al.*, in: *Befol, a New Original Russian-Manufactured Antidepressant* [in Russian], Moscow (1990), pp. 57-68.
11. G. F. Lakin, *Biometry* [in Russian], Moscow (1980).
12. N. B. Leonidov, P. A. Galenko-Yaroshevskii, Yu. R. Sheikh-Zade, *et al., Byull. Eksp. Biol. Med.*, **124**, No. 7, 77-80 (1997).
13. P. V. Sergeev, P. A. Galenko-Yaroshevskii, A. I. Khankoeva, A. S. Dukhanin, *Ibid.*, **121**, No. 3, 288-291 (1996).
14. V. V. Skibitskii, *Pharmacological Activation of Stress-Limiting System in the Therapy of Cardiac Rhythm Disturbances*. Abstr. of Ph.D. Thesis, Moscow (1993).
15. A. I. Khankoeva, *Approaches to Diminish Cardiotoxicity of Antiarrhythmic Drugs in Ischemic Myocardium*. Abstr. of PhD Thesis, Rostov-on-Don (1995).
16. A. I.Khankoeva, P. A. Galenko-Yaroshevskii, and A. S. Dukhanin, *Byull. Eksp. Biol. Med.*, **123**, No. 5, 45-47 (1997).