Correction of Cardiotoxic Effects of Cardiac Antiarrhythmics with Befol, Suphan, and Their Combinations

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Antidepressant befol, non-glycoside cardiotonic suphan, and their combinations were shown to have different ability to decrease cardiotoxic (arrhythmogenic) effect of novocainamide, lidocaine, bonnecor, obsidan, cordarone, verapamil, and rhythmidazol.

Key Words: *cardiac antiarrhythmics; cardiotoxic effect; befol; suphan;*

The cardiovascular system plays a basic role in transport, deposition, and metabolism of cardiac antiarrhythmics and other preparations [11]. Changes in kinetics of antiarrhythmic preparations occur in various diseases of cardiovascular system, which may result in overdose and toxic manifestations, mostly cardiac, which are expressed in "paradoxical" appearance of cardiac rhythm and in weakening of myocardial activity, which may cause sudden death [5,11].

In many cases cardiotoxic effects (CTE) of cardiac antiarrhythmics stem from their potency to disturb energy and ionic exchange as well as myocardial ultrastructure [5,10].

Activators of central stress-limiting systems (including the agents increasing serotonin content in central nervous system), which liquidate the energy-deficient states (intermediate substances of Krebs cycle; specifically, succinic acid and its derivatives) decrease ischemic damage to the myocardium, normalize electrical instability of the heart, and exhibit antianginal activity [2,6,9,15].

An original drug befol (4-chlorine-N-(3-morpholinopropyl)-benzamide hydrochloride), a reversible antidepressant that inhibits type A monoaminoxidase with serotonin as a substrate [1], exerts antiarrhythmic effect in patients with ventricular extrasystoles against the background of neurocirculatory dystonia and myocardial ischemia [4]. In addition, befol activates the antioxidant system in erythrocytes and decreases serum level of lipid peroxidation [12].

A new synthetic drug suphan (bipotassium salt of N-succinyl-dl-tryptophan, a nonglycoside cardiotonic) produces antianginal effects and normalizes energy exchange and ultrastructural organization of the myocardium subjected to acute hypoxic hypoxia in animals [3,10].

Our aim was to search for the ways to decrease CTE of antiarrhythmics grouped into different classes according to [16]: novocainamide (IA), lidocaine (IB), bonnecor (IC), obsidan (II), cordarone (III), verapamil (IV), and also a new antiarrhythmic preparation rhythmidazol (dihydrochloride-9-diethylaminoethyl-2-tertiarobutilimidazo(1,2-α) benzimidazole), in their combinations with befol and suphan. Rhythmidazol has the properties of antiarrhythmics of the I, III, and IV classes and is permitted for clinical testing as an antiarrhythmic drug (Permission of Pharmacological Committee of Russian Ministry of Health, November 18, 1993, No. 211-15/2500).

MATERIALS AND METHODS

Experiments were performed on 1963 non-narcotized male Wistar rats. In order to study combined action

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of the antiarrhythmics befol and suphan we used the method described in [13,14] modified as in [7]. The mean cardiotoxic dose (CTD_{50}) was determined, in which a substance injected intravenously induced arrhythmias in 50% animals [8]. Then CTD_{50} for each test substance was determined when it was injected in combination with the other (background substance). The ratio of the second CTD_{50} value to the first one was assumed as a protection coefficient (PC). The ECG (standard lead II) recorded with an EKIT-04 electrocardiograph. The results were processed made using specially designed original software.

RESULTS

Estimated CTD_{50} for befol, suphan, novocainamide, lidocaine, bonnecor, obsidan, cordarone, verapamil, and rhythmidazol were as follows: 186, 89, 97, 31, 2.3, 15.4, 154, 1.2, and 24.7 mg/kg, respectively.

Figure 1, *a* shows that the interaction between suphan and befol can be interpreted as synergism-antagonism (predominantly, as absolute antagonism). Suphan in low doses of $^1/_4$ and $^1/_2$ CTD_{50} is an absolute antagonist of befol, while in higher doses ($^3/_4$ and 1 CTD_{50}) it demonstrates a relative antagonism.

The effect of befol-novocainamide combination can be described as absolute antagonism, which is enhanced with an increase in befol dose to $^1/_2$ CTD_{50}. However, at higher doses this antagonism drastically reduces and at doses higher than $^3/_4$ CTD_{50} it turns into the relative antagonism. When suphan was used as a background substance (BS), a characteristic tendency was a relative antagonism with novocainamide; only when suphan was given in a dose of $^1/_4$ CTD_{50}, the absolute antagonism was observed. It is noteworthy that when BS was novocainamide, it demonstrated a pronounced absolute antagonism to suphan (PC=3.48).

In the study of suphan and befol combinations to correct CTE of novocainamide it was established (Fig. 1, *b*) that the maximum protective effect of both BS (PC=1.69) is attained when they are administered at $^1/_4$ CTD_{50}.

Interaction of suphan with lidocaine is characterized by relative antagonism and a moderate absolute antagonism. When lidocaine was a BS, a very pronounced absolute antagonism was observed (PC= 3.66). Combined action of befol and lidocaine showed mutual relative antagonism (Fig. 2, *1, a*).

Combination of suphan and befol has no significant protective effect in respect to CTE of lidocaine. The maximum increase in PC (to 1.44 and 1.39) was observed when $^1/_4$ CTD_{50} suphan was given with befol in doses of $^3/_4$ or 1/4 CTD_{50}, respectively. In doses of about 1 CTD_{50} suphan and befol decreased their protective effect against CTE of lidocaine (Fig. 2, *1, b*).

Interaction of suphan with bonnecor can be interpreted as an absolute antagonism (in a dose of

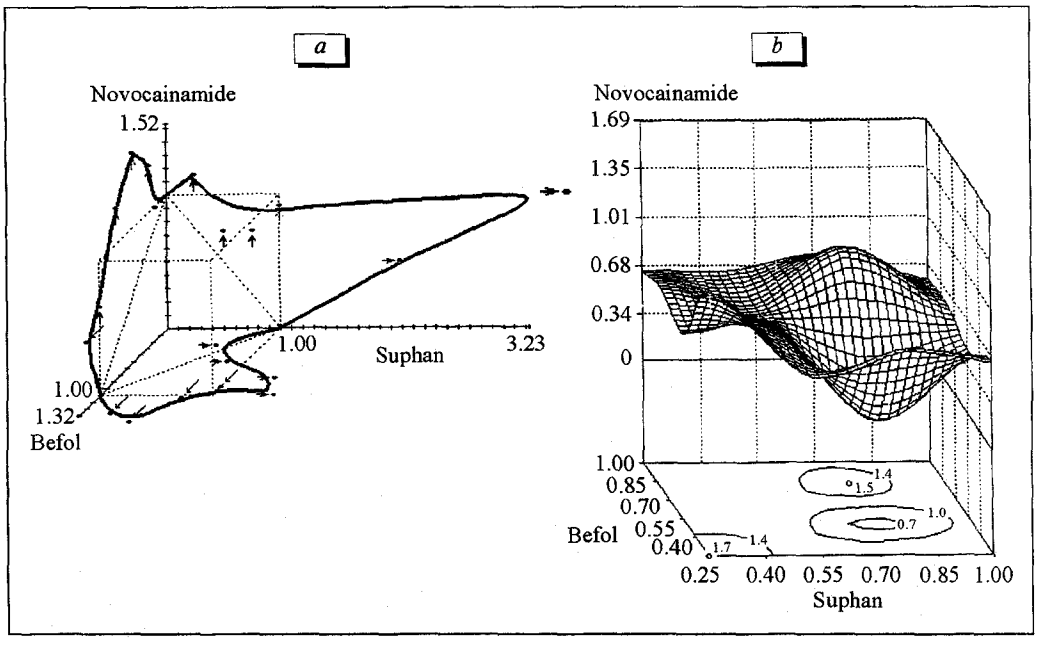

Fig 1. Reduction of antiarrhythmic effect of novocainamide by befol, suphan, and their combinations. Here, and in Figs. 2 and 3, isobolograms of the interactions between an antiarrhythmic, befol, and suphan are shown (*a*). The interactions between pairs of substances are shown in 3-D plots. Ordinate, abscissa: relative preparation doses in CTD_{50} units; efficacy of befol/suphan combination in protection of arrhythmogenic effect of an antiarrhythmic represented as 3-D diagram (*b*). Axes on the isodynamic diagram (the bottom of the plot) are the relative doses in CTD_{50} units, the numbers and isolines at the bottom show the protection coefficients of combinations. Z axis: protection coefficients for combinations of an antiarrhythmic, suphan, and befol.

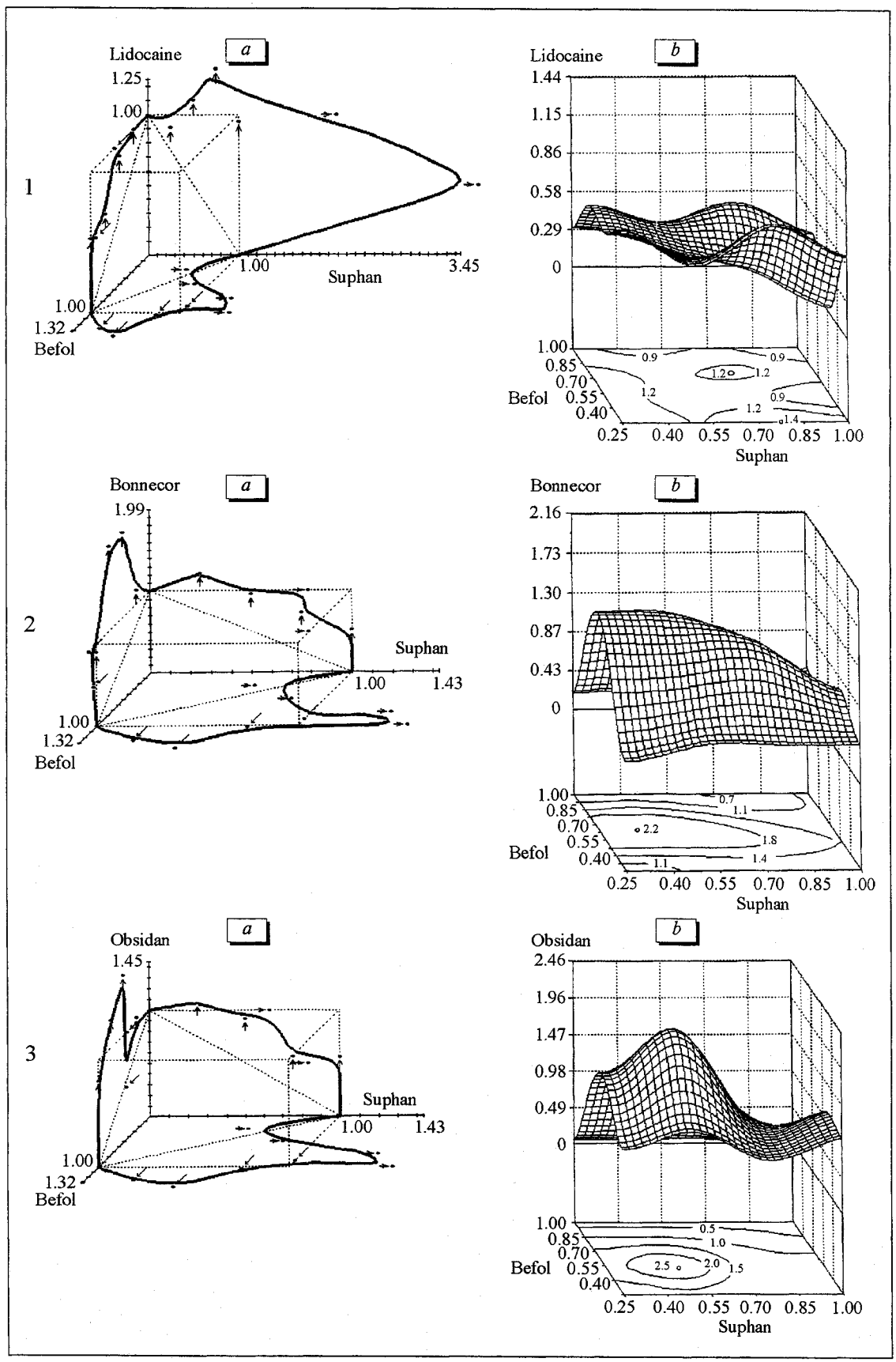

Fig 2. Reduction of antiarrhythmic effect of lidocaine (*1*), bonnecor (2), and obsidan (3) by befol, suphan, and their combinations.

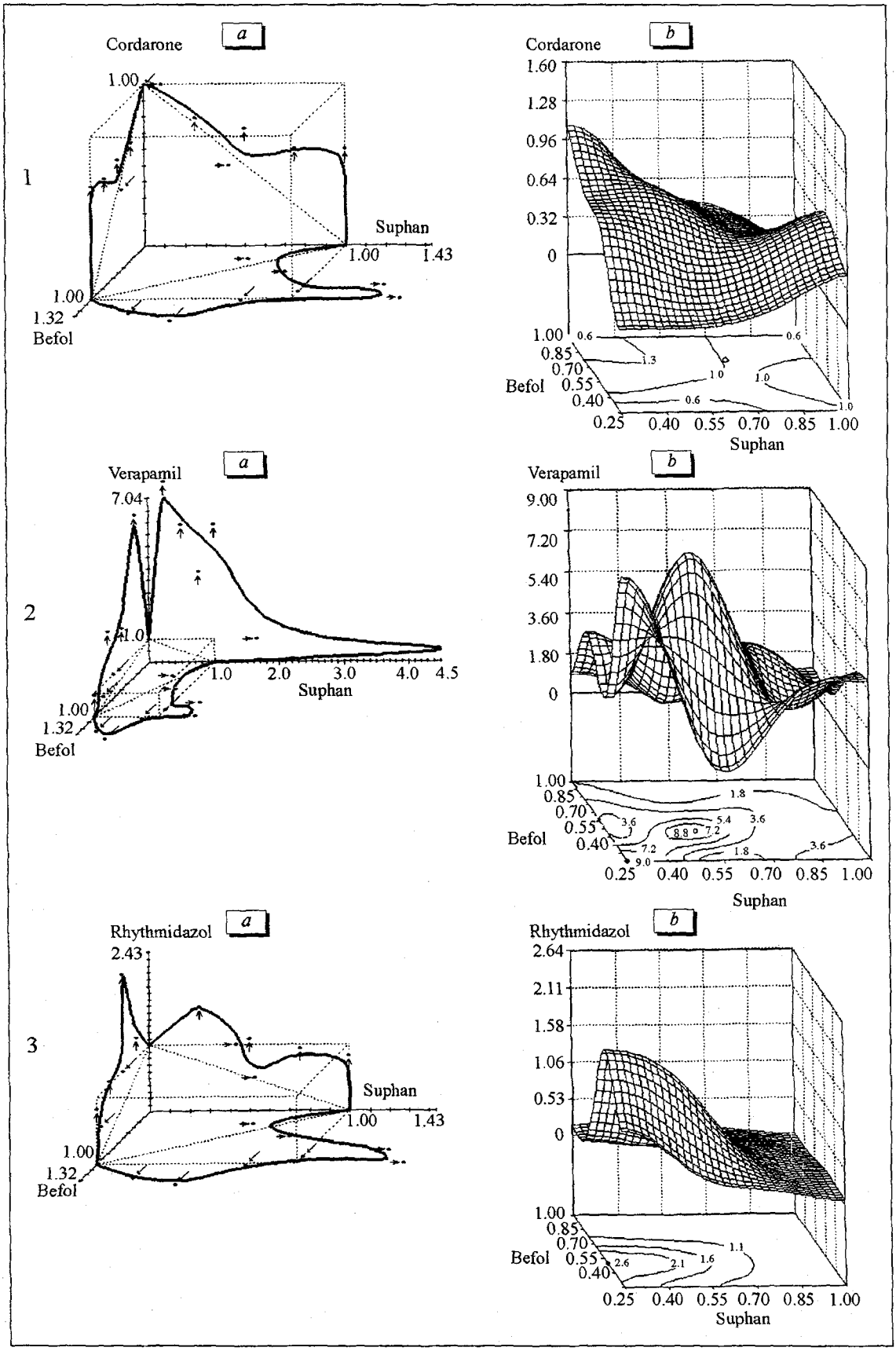

Fig 3. Reduction of antiarrhythmic effect of cordarone (*1*), verapamil (2), rhythmidazol (3) by befol, suphan, and their combinations.

$^1/_4$ CTD_{50} befol) which turns into relative antagonism when the dose is increased. Combination of befol with bonnecor is an example of a marked mutual absolute antagonism. It is noteworthy that the maximum protective effect of befol takes place in its dose of $^1/_2$ and $^3/_4$ CTD_{50} (Fig. 2, *2, a*).

When combinations of suphan with befol were tested for prevention of CTE of bonnecor, the most significant cardioprotective effect was exerted by the combination of $^3/_4$ CTD_{50} befol and $^1/_4$ or $^1/_2$ CTD_{50} suphan. In both cases PC was 1.96. Both increase and decrease of the above-mentioned effective doses of suphan and befol decreased protective effect of these drugs (Fig. 2, *2, b*).

Combinations of suphan with obsidan demonstrated a bilateral relative antagonism. When suphan was given in a dose of $^1/_4$ CTD_{50}, a tendency toward absolute antagonism was observed. Interrelations of befol and obsidan are characterized by relative antagonism (in a dose of $^1/_4$ CTD_{50} befol), which turns into the absolute antagonism (from $^1/_2$ CTD_{50} befol). Further increase in a befol dose to 1 CTD_{50} is characterized by return to relative antagonism (Fig. 2, *3, a*).

Study of the possibility to correct CTE of obsidan with combinations of befol and suphan showed that the maximum protective effect (PC=2.4) occurs when both BS are injected in a dose of $^1/_2$ CTD_{50} (Fig. 2, *3, b*).

Combinations of befol or suphan with cordarone were characterized by a tendency to additivity (when BS were given in small doses, i.e., up to $^1/_2$ CTD_{50}), which turned into relative antagonism with increased BS doses. In all cases PC<1 (Fig. 3, *1, a*).

Cardioprotective effect of the suphan/befol combination against CTE of cordarone was most pronounced (PC=1.60) when they were used in the doses of $^1/_4$ and 1 CTD_{50}, respectively (Fig. 3, *1, b*).

Combination of suphan with verapamil is characterized by mutual absolute antagonism. It is noteworthy that verapamil in a dose of $^1/_2$ CTD_{50} enhances CTD_{50} of suphan, PC being 5.26. Combination of befol with verapamil is described as a unilateral absolute antagonism (Fig. 3, *2, a*).

When combinations of suphan with befol were tested to prevent CTE of verapamil, the most pronounced protective effects of background substances were observed when they were combined in relatively small doses: $^1/_4$ and 1/2 CTD_{50} (Fig. 3, *2, b*).

Interaction of befol with rhythmidazol was characterized by unilateral absolute antagonism, which increased with befol doses ranging from $^1/_4$ to $^1/_2$ CTD_{50} (46.5-93.0 mg/kg), but drastically decreased with an increase in befol doses from $^1/_2$ to $^3/_4$ CTD_{50} (93.0-139.5 mg/kg). Further increase in befol doses (from $^3/_4$ to 1 CTD_{50}) resulted in transition to relative antagonism (Fig. 3, *3, a*). The most pronounced cardioprotective effect of befol was observed in a dose of 93 mg/kg ($^1/_2$ CTD_{50}) with PC=2.48.

Interaction of suphan with rhythmidazol can be described as a unilateral absolute antagonism (when suphan doses were small: $^1/_4$-$^1/_2$ CTD_{50} or 22.3-44.5 mg/kg), which turned into relative antagonism with dose increase (Fig. 3, *3, a*). The maximum protective effect of suphan was observed in a dose of 22.3 mg/kg ($^1/_4$ CTD_{50}); CTD_{50} of rhythmidazol increased from 24.7 to 39.1 mg/kg with PC=1.58. In doses lower than $^1/_4$ CTD_{50} ($^1/_8$, $^1/_{16}$ CTD_{50}) suphan had no protective effect, while in doses higher than $^1/_2$ CTD_{50} ($^3/_4$ and 1 CTD_{50}) it potentiated cardiotoxic effect of rhythmidazol in a dose-dependent manner.

When befol and suphan were administered in combination, the maximum cardioprotective effect against CTE of rhythmidazol was observed when befol and suphan were combined at $^1/_4$ CTD_{50} (46.5 mg/kg) and $^1/_2$ CTD_{50} (44.5 mg/kg), respectively (Fig. 3, *3, b*).

Thus, novocainamide, lidocaine, bonnecor, obsidian, cordarone, verapamil, and rhythmidazol have cardiotoxic effect in certain doses. Cordarone and, in particular, lidocaine, manifest CTE in much more higher doses (when isotoxic doses are compared) then other antiarrhythmics tested in this work.

Befol, suphan, and their combinations display cardioprotective activity varying in extent against CTE of novocainamide, lidocaine, bonnecor, obsidian, cordarone, verapamil, and rhythmidazol, demonstrating both relative and absolute antagonism in respect to these drugs; in some cases there were manifestations of additive action and synergism-antagonism. Novocainamide, lidocaine, and verapamil drastically decrease CTE of suphan.

Protective effect of befol and suphan observed during cardiac arrhythmias caused by cardiotoxic doses of the studied antiarrhythmic drugs may be related to their ability to directly or indirectly accumulate serotonin in the central nervous system, to liquidate energy-deficient states in the myocardium, thereby activating central and peripheral stress-limiting systems [1,9,10]. It cannot be excluded that cardioprotective effect of befol and suphan is mediated by their influence on coronary circulation, oxygen consumption in the myocardium, and transmembrane ionic currents in cardiomyocytes [3,10].

The data obtained can be used to decrease CTE of cardiac antiarrhythmics.

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REFERENCES

1. E. M. Gankina, M. F. Mineeva, D. Yu. Rusakov *et al.*, In: *A New Original Antidepressant Befol* [in Russian], 69-87, Moscow (1990).
2. V. V. Gatsura, *Pharmacological Correction of Energy Exchange in the Ischemic Myocardium* [in Russian], Moscow (1993).
3. A. I. Grinevich, I. S. Checkman, P. A. Galenko-Yaroshevskii *et al*, *Dokl. AN Ukrainy*, No. 5, 169-173 (1994).
4. S. G. Kanorskii, *Combinatory Pharmacotherapy with Antiarrhythmics and Psychotropic Drugs With the Help of Electrophysiological Tests* [in Russian], Abstr. of Ph. D. Thesis, Krasnodar (1993).
5. M. S. Kushakovskii, *Cardiac Arrhythmias* [in Russian], St. Petersburg (1992).
6. F. Z. Meerson, M. G. Pshennikova, *Adaptation to Stress and Physical* Loads, Moscow (1988).
7. V. B. Prozorovskii, *Farmakol. Toksilkol.*, No. 2, 33-37 (1984).
8. V. B. Prozorovskii and M. P. Prozorovskaya, *Farmakol. Toksikol.*, **43**, No. 6, 733-735 (1980).
9. V. V. Skibitskii, *Pharmacological Activation of Stress Limiting Systems in Arrhythmia Therapy*, Abstr. of M. D. Thesis, Moscow (1995).
10. A. I. Khankoeva, *A Study of Ways of Diminishing Cardiotoxic effect of Antiarrhythmics in Myocardial Ischemia Conditions*, Abstr. of Ph. D. Thesis, Rostov-on -Don (1995).
11. L. E. Kholodov, V. P. Yakovlev, *Clinical Pharmacokinetics* [in Russian], Moscow (1985).
12. Yu. K. Chipizubov, *Lipid Peroxidation and Antioxidant Blood Activity in Patients with Arrhythmias In the Course of Pharmacotherapy* [in Russian], Abstr. of Ph. D. Thesis, Krasnodar (1993).
13. S. Loewe, *Ergebn. Physiol.*, **27**, 47 (1928).
14. S. Loewe, *Pharmacol. Rev.*, **9**, 237-242 (1957).
15. B. Lown, R. Dasilova, P. Reich, and B. Murawski, *Am. J. Psychiatry*, **137**, No. 11, 1325-1335 (1980).
15. E. M. Vaughan Williams, *Clinical Pharmacol.*, **24**, No. 1, 129-147 (1984).