PHARMACOLOGY AND TOXICOLOGY

Cardiotoxic Effects of the Antiarrhythmic Rhythmidazol and Their Correction by Suphan, Befol, and Their Combinations

P. A. Galenko-Yaroshevskii, V. V. Skibitskii, V. B. Boldin, M. M. Seredenko, A. I. Khankoeva, and A. V. Uvarov

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 124, No. 12, pp. 640-644, December, 1997
Original article submitted January 22, 1997

The antiarrhythmic rhythmidazol produces a cardiotoxic effect that can be corrected by suphan, befol, and their combinations, as evidenced by normalization of ultrastructural organization of cardiomyocytes and myocardial oxygen consumption by these drugs.

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

Along with nominal therapeutic effects, antiarrhythmic drugs produce cardiotoxic effects (CTE) that manifest themselves in the appearance of new and in many cases fatal cardiac rhythm disturbances and in the inhibition of myocardial contractility [3,7,11].

Morphological basis of CTE of antiarrhythmic drugs is provided by changes in myocardial ultrastructural organization (MUSO) [7,11], which are conjugated with ionic imbalance and disturbance of oxygen consumption in cardiomyocytes [1].

Both the nonglycoside cardiotonic suphan (N-succine-dl-tryptophan dipotassium salt) and the reversible monoamine oxidase inhibitor antidepressant befol have pronounced cardioprotective effect against CTE of such standard antiarrhythmic drugs as procainamide, lidocaine, bonnecor, Obsidan, and verapamil [7].

Thus, it seems worthwhile to study CTE of the new antiarrhythmic drug rhythmidazol (dihydrochloride-9-diethylaminoethyl-2-tertiarobytilimidazo(1,2-a) benzimidazole), which according to classification [12] belongs to classes I and III antiarrhythmic drugs [5]. It should be necessary to test the possibility of correcting CTE of this antiarrhythmic drug by suphan, befol, and their combinations and to examine the effects of these preparations on MUSO and myocardial oxygen consumption.

MATERIALS AND METHODS

The study was carried out on 427 conscious male albino rats. Combined action of rhythmidazol, befol, and suphan was tested by the method [10,11] with modifications [4]. The mean cardiotoxic doses (CTD_{50}) of the drugs were determined by their intravenous administration in doses provoking arrhythmia in 50% of animals. Arrhythmias were estimated by ECG (standard lead II). Befol, suphan, and their combinations in different doses (1/4, 1/2, 3/4, and 1 CTD_{50}) were administered 5 min prior to rhythmidazol. The ratio of the new CTD_{50} value to the control was taken as the protection coefficient (PC).

The effects of the drugs on oxygen consumption and MUSO were studied in rats under acute hypoxia

Department of Pharmacology, Department of Hospital Therapy and Clinical Pharmacology, Kuban Medical Academy, Krasnodar; Department of Hypoxia Research, A. A. Bogomolets Physiology Institute, Kiev

0007-4888/97/0012-1189$18.00

TABLE 1. Mean CTD_{50} of the Test Drugs and PC of the Background Substances in the Combined Action of Rhythmidazol, Suphan, and Befol in the Experiments in Conscious Rats (n=12)

Background substance		Test drug		PC
name	dose/CTD_{50}	name	CTD_{50}, mg/kg	
Control		Rhythmidazol	24.7 (22.0÷28.0)	1.0
		Befol	186.0 (170.0÷200.0)	1.0
		Suphan	89.0 (67.0÷118.0)	1.0
Befol	1/4 [46.5]	Rhythmidazol	32.6 (29.0÷37.0)	1.32
	1/2 [93.0]		61.2 (54.0÷70.0)	a2.48
	3/4 [139.5]		26.1 (22.0÷31.0)	1.06
	1		20.8 (18.0÷24.0)	0.84
Rhythmidazol	1/2 [12.4]	Befol	172.0 (150.0÷190.0)	0.92
	1		93.0 (75.0÷117.0)	0.50
Suphan	1/4 [22.3]	Rhythmidazol	39.1 (34.0÷45.0)	1.58
	1/2 [44.5]		27.2 (24.0÷31.0)	1.10
	3/4 [66.8]		23.4 (21.0÷25.0)	0.95
	1		20.6 (18.0÷23.0)	0.83
Rhythmidazol	1/2 [12.4]	Suphan	46.8 (39.0÷58.0)	0.53
	1		38.7 (34.0÷44.0)	0.43
Befol	1/4 [46.5]	Suphan	51.7 (46.0÷59.0)	0.58
	1/2 [93.0]		74.1 (69.0÷81.0)	0.83
	3/4 [139.5]		124.0 (110.0÷140.0)	1.39
	1		137.0 (120.0÷150.0)	1.54
Suphan	1/4 [22.3]	Befol	234.0 (190.0÷290.0)	1.26
	1/2 [44.5]		261.0 (220.0÷310.0)	1.4
	3/4 [66.8]		191.0 (161.0÷230.0)	1.03
	1		164.0 (140.0÷190.0)	0.88

Note. Dose relative to CTD_{50} is given in brackets. The confidence levels at p=0.05 are given in parentheses. PC was estimated as the ratio of control CTD_{50} to test value.

(30 min, 6.8% oxygen in nitrogen gas). Oxygen consumption was determined by Warburg's manometry after decapitation of rats, isolation of myocardium, and grinding it on ice.

Fragments of the right and left ventricular myocardium were examined and processed according to [6]. Ultrathin sections were stained with uranyl acetate and lead citrate, and then examined in a JEM-100CX electron microscope.

RESULTS

CTD_{50} of rhythmidazol is 24.7 mg/kg (Table 1). Befol demonstrated absolute unilateral antagonism with rhythmidazol (Fig. 1) which increased in the dose range of 1/4 to 1/2 CTD_{50} (46.5-93.0 mg/kg) and then drastically decreased in the range of 1/2 to 3/4 CTD_{50} (93.0-139.5 mg/kg). Further increase in befol dose (3/4 to 1 CTD_{50}) coincided with transition to unilateral relative antagonism. The strongest cardioprotective effect of befol was observed at 93.0 mg/kg (1/2 CTD_{50}), which corresponded to PC 2.48.

At small doses of suphan (1/4-1/2 CTD_{50} or 22.3-44.5 mg/kg) interaction of suphan with rhythmidazol can be described as a phenomenon of absolute unilateral antagonism, which turns into relative antagonism with further rise of suphan dose (Fig. 2). The maximum protective effect of suphan was observed in a dose of 22.3 mg/kg (1/4 CTD_{50}), which led to enhancement of CTD_{50} from 24.7 to 39.1 mg/kg (PC=1.58). In doses lower than 1/4 CTD_{50} (1/8 and 1/16 CTD_{50}) suphan did not produce 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.

Study of the relationships between befol and suphan showed that given in dose of 1/4 and particularly in dose of 1/2 CTD_{50} (22.3 and 44.5 mg/kg, respectively) suphan increased the CTD_{50} of befol (PC=1.26 and 1.40, respectively), thereby demon-

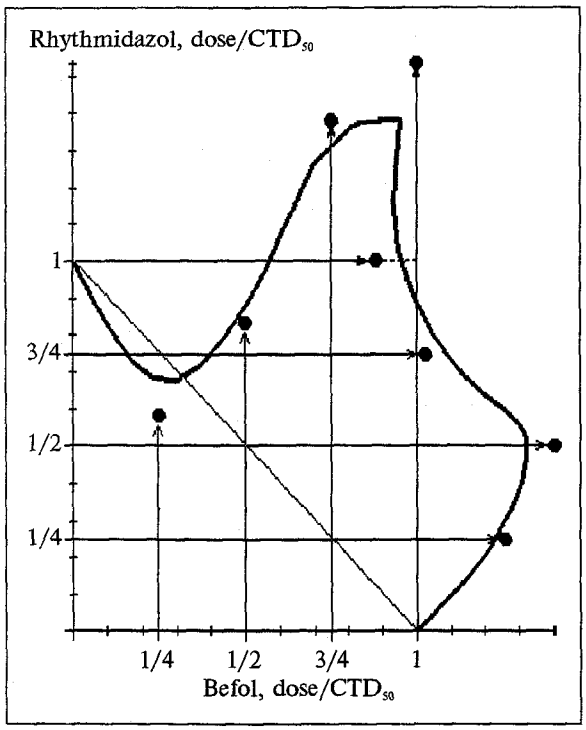

Fig. 1. Isobologram of interaction of rhythmidazol and befol administered intravenously to conscious rats at a 2-min interval.

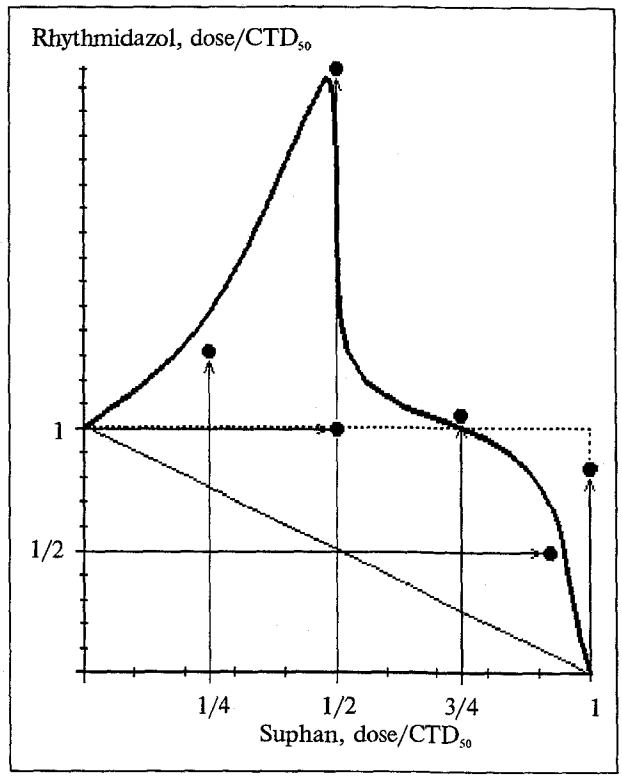

Fig. 2. Isobologram of interaction of rhythmidazol and suphan administered intravenously to conscious rats at a 2-min interval.

strating the absolute antagonism (Fig. 3). Small doses of befol were summarized with the larger ones of suphan according to the principle of complete summation resulting in the additive effect. With an increase in befol dose this summation initially becomes partial and then it is replaced by absolute antagonism. The maximum protective effect of befol in respect to suphan (PC=1.54) was manifested in a dose of 186.0 mg/kg (1 CTD_{50}), while that of suphan in respect to befol in a dose of 44.5 mg/kg (1/2 CTD_{50}).

Our next aim was to evaluate the possibility of enhancing myocardial resistance to cardiotoxic effect of rhythmidazol using combined administration of befol and suphan in different doses (1/4, 1/2, 3/4, and 1 CTD_{50}, Table 2). The maximum cardioprotective effect (PC=2.64) was observed with the combination of 1/4 CTD_{50} befol (46.5 mg/kg) and 1/2 CTD_{50} suphan (44.5 mg/kg).

Thus, there is a possibility for optimal correction of cardiotoxic effect of rhythmidazol by combined administration of befol (1/4 CTD_{50}) and suphan (1/2 CTD_{50}).

The results obtained served as a basis to study the effect of this combination on MUSO and myocardial oxygen consumption during acute hypoxic hypoxia.

It was found that combined administration of rhythmidazol, befol, and suphan in hypoxia prevented the development of oxygen debt, which was

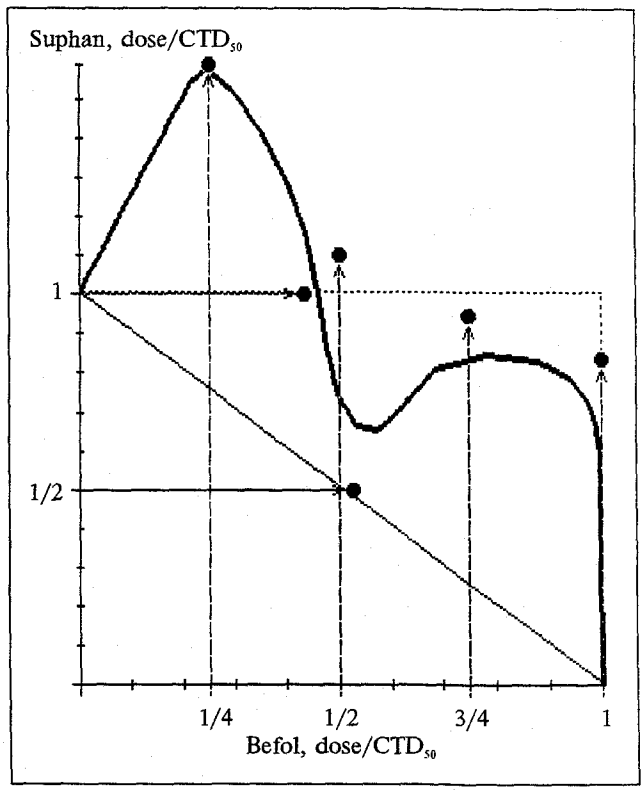

Fig. 3. Isobologram of interaction of suphan and befol administered intravenously to conscious rats at a 2-min interval.

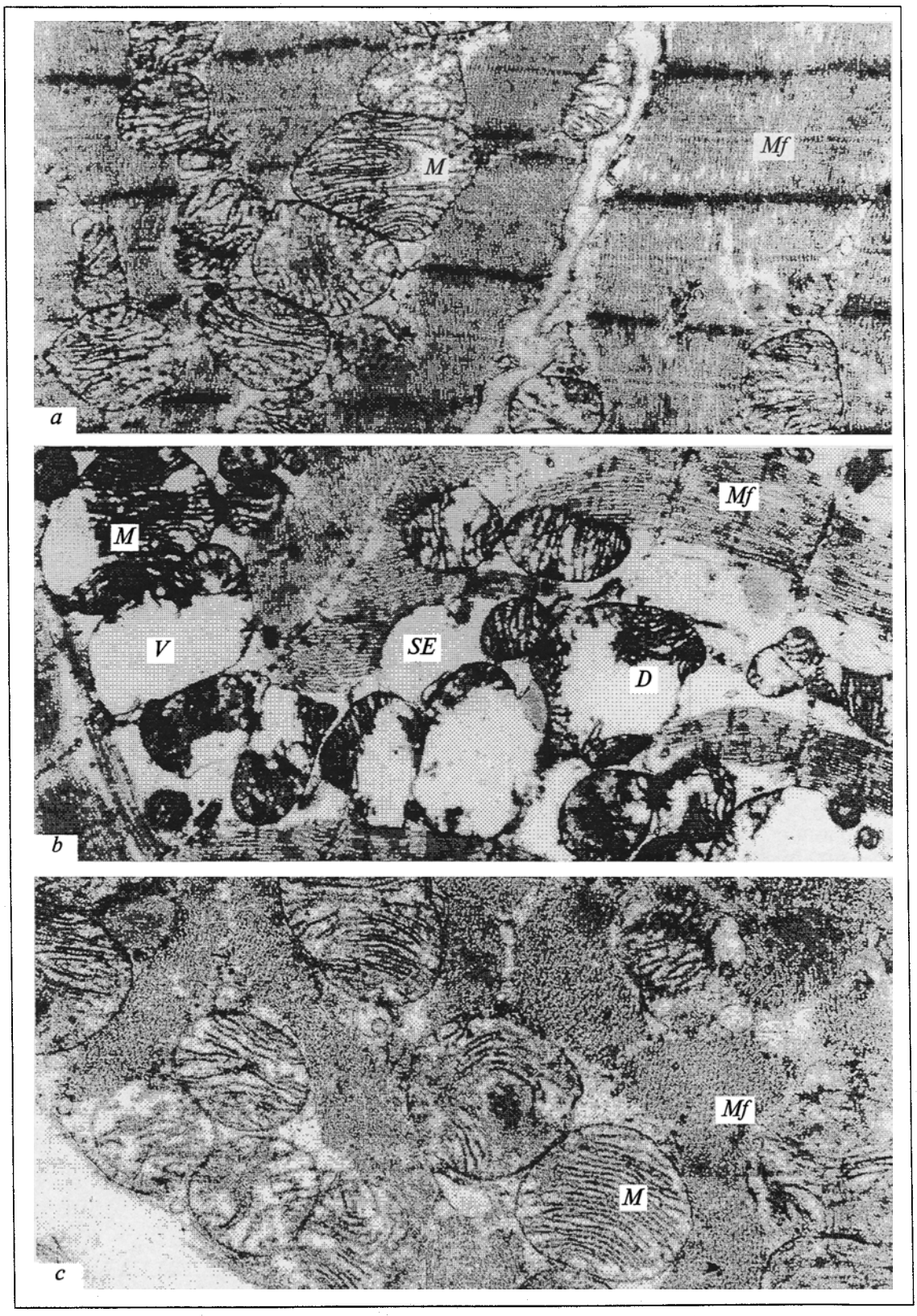

Fig. 4. Ultrastructure of rat myocardium, ×14,000. *a*) normoxia (control); *b*) acute hypoxic hypoxia; *c*) administration of rhythmidazol (24.7 mg/kg) and suphan (44.5 mg/kg), and befol (46.5 mg/kg) followed by acute hypoxic hypoxia. *M*) mitochondrion, *Mf*) myofibrils, *V*) vacuolation, *D*) destruction, *SE*) sarcoplasmic edema.

TABLE 2. CTD_{50} by Cardiotoxic (Arrhythmogenic) Effect of Rhythmidazol after Preliminary (5 min) Intravenous Administration of Befol and Suphan (n=12)

Befol, dose/CTD_{50}	Suphan, dose/CTD_{50}			
	1/4 (1.58)	1/2 (1.10)	3/4 (0.95)	1 (0.83)
1/4 (1.32)	1.81	2.64	1.14	0.87
1/2 (2.48)	1.19	2.20	0.97	0.95
3/4 (1.06)	0.95	1.05	0.97	0.83
1 (0.84)	0.79	0.83	0.75	0.72

Note. PC values with respect to rhythmidazol are given in parentheses.

TABLE 3. Effect of Combined Administration of Rhythmidazol with Suphan and Befol on Myocardial Oxygen Consumption in Acute Hypoxic Hypoxia (n=10)

Experimental series	Myocardial oxygen consumption, μl/h/mg dry matter
Initial state	4.8±0.1
Acute hypoxia	6.0±0.3
Rhythmidazol (24.7 mg/kg)+suphan (44.5 mg/kg)+befol (46.5 mg/kg)+hypoxia	4.7±0.1*

Note. *p<0.05 with respect to hypoxia.

manifested as a decrease in myocardial oxygen consumption by 21.7% (Table 3), and in addition, it limited the development of acute hypoxic changes in the myocardium (Fig. 4). Significant improvements in ultrastructure of cardiomyocytes and hematoparenchymatous barrier were observed. There were no signs of edema in the endotheliocytes of microvessels. The size of the sites of destruction of the hematoparenchymatous barrier decreased. Enhanced pinocytosis in endotheliocytes can be interpreted as a sign of intensification of tissue metabolism [9]. An essential normalization of mitochondrial ultrastructure took place, the regularity of cristae was restored, while no signs of membrane destruction were present. In some mitochondria, clarification of the matrix occurred with the signs of swelling.

Thus, the present study revealed cardiotoxic effect of rhythmidazol, showed the possibility of its correction by suphan and befol, and demonstrated conjugation of cardioprotective potency of rhythmidazol, suphan, and befol combination with its antihypoxic effect and normalizing influence on MUSO.

We are grateful to Dr. I. S. Chekman for the generous gift of rhythmidazol.

REFERENCES

1. V. V. Gatsura, *Pharmacological Correction of Energy Exchange in the Ischemic Myocardium* [in Russian], Moscow (1993).
2. A. I. Grinevich, I. S. Chekman, P. A. Galenko-Yaroshevskii, *et al.*, *Dopov. Akad. Nauk Ukraine*, No. 5, 169-173 (1994).
3. M. S. Kushakovskii, *Cardiac Arrhythmias* [in Russian], St. Petersburg (1992).
4. V. B. Prozorovskii and M. P. Prozorovskaya, *Farmakol. Toksikol.*, **43**, No. 6, 733-735 (1980).
5. V. V. Skibitskii, P. A. Galenko-Yaroshevskii, S. G. Kanorskii, *et al.*, *Vestn. Aritmol.*, No. 4, 227 (1995).
6. B. S. Weakley, *Essentials of Electron Microscopy in Biology* [Russian translation], Moscow (1975).
7. A. I. Khankoeva, "A search for methods of moderation of cardiotoxic effects of antiarrhythmic drugs on the ischemic myocardium", Author's Synopsis of PhD Dissertation [in Russian], Rostov-on-Don (1995).
8. L. E. Kholodov and V. P. Yakovlev, *Clinical Pharmacology* [in Russian], Moscow (1985).
9. V. A. Shakhlamov, *Capillaries* [in Russian], Moscow (1971).
10. S. Loewe, *Ergebh. Physiol.*, **27**, 47 (1928).
11. S. Loewe, *Pharmacol. Rev.*, **3**, 237-242 (1957).
12. E. M. Vaughan-Williams, *J. Clin. Pharmacol.*, **24**, No. 1, 129-147 (1984).