lar compounds may be one more piece of evidence of the possibility of axonal transport of radioactive histone in the olfactory system structures.

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PHARMACOLOGY

Drug Correction of Impaired Strophanthin Tolerance during Simulated Cardiac Decompensation

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The risk of glycoside intoxication under conditions of simulated acute and subacute cardiac insufficiency may be reduced by ajmaline, anaprilin, and combinations of each of these drugs with pentamine or nitroglycerin.

Key Words: *correction of strophanthin toxicity, cardiac insufficiency*

Administration of cardiac glycosides representing the main group of cardiotonic agents for emergency use in acute cardiac failure caused by coronary heart disease, for example, sometimes does not result in adequate improvement of myocardial contractility and recovery of impaired hemodynamics. The therapeutic effect of glycoside cardiotonics is limited by a sharply increased sensitivity to their toxic action [3,10,11]. Since management of heart failure envisages that, in addition to cardiac glycosides, quite a number of other drugs be used, indicated individually for each specific clinical situation, we thought it interesting to test on models of acute and subacute cardiac insufficiency the effects of some drug combinations most frequently used in clinical cardiology on tolerance for the toxic effect of strophanthin.

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MATERIALS AND METHODS

Experiments were carried out with 385 Wistar rats weighing 160-170 g narcotized with sodium thio-

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pental, 40 mg/kg intraperitoneally. Cardiac failure in experimental rats was induced by two methods [2]: overexertion by swimming till exhaustion, which led to the development of acute heart failure, and histotoxic exposure to high doses of the β-adrenomimetic isoprenaline, which caused the development of subacute cardiac insufficiency. The existence of cardiac insufficiency in animals was confirmed by the appearance of hemodynamic disturbances typical of this condition, the anatomicohistological picture of the viscera, the myocardial electrolyte balance, and changed tolerance for the arrhythmogenic and general toxic effect of strophanthin. Hemodynamic parameters were recorded by the thermodilution method [4,7], the electrolyte content in the myocardium was assessed by flame photometry using a BIAN-140 photometer [6], morphological changes were examined macro- and microscopically, and slices were stained with hematoxylin-eosin. Strophanthin tolerance was assessed by biological titration of its minimal arrhythmogenic dose (MAD) and lethal dose (LD) [2] in 27 experimental series: in intact animals (control), in acute and subacute cardiac insufficiency, and under the same experimental conditions in the presence of premedication with anaprilin (5 mg/kg), ajmaline (5 mg/kg), pentamin (3 mg/kg), and nitroglycerin (0.5 mg/kg), and with some combinations of these drugs in similar doses (anaprilin+pentamin, ajmaline + pentamin, anaprilin+nitroglycerin, ajmaline+nitroglycerin). The drugs were injected intravenously 5 min before starting titration of strophanthin toxic doses. Results were processed by routine methods of variational statistics [5].

RESULTS

Our data indicate that overexertion of experimental animals till exhaustion and the histotoxic action of high doses of the β-adrenomimetic isoprenaline lead to the development of, respectively, acute and subacute cardiac insufficiency. The chosen models of cardiac insufficiency were characterized by changes in hemodynamics typical of this condition, the myocardial electrolyte balance, and disorders of the anatomicohistological picture of the viscera with the development of congestive phenomena in the lesser and greater circulation. Irrespective of the method of cardiac insufficiency induction, the animals developed an approximately twofold reduction of the stroke and minute blood volumes, increase of total peripheral vascular resistance, and a noticeable reduction of the parameters characterizing the contractile function of the heart: cardiac and systolic indexes and left-ventricular work (Fig. 1). The K^+ level in myocardial cells of animals with acute and subacute cardiac insufficiency decreased more than twofold, whereas the Na^+ content increased to the same extent. The coefficient K^+/Na^+, indicating the ionic balance in cardiomyocytes, was reduced more than fivefold during both modes of cardiac insufficiency simulation. Table 1 shows that tolerance for the arrhythmogenic and general toxic effect of strophanthin was markedly reduced in experimental animals, its MAD and LD decreasing by 34.3 and 22.0% in acute heart failure and by 34.3 and 19.9% in the subacute condition, respectively.

Premedication with combinations of drugs indicated, along with cardiac glycosides, in emergency clinical situations had a variable protective effect on the hypersensitivity to the toxic action of strophanthin which is characteristic of cardiac decompensation (Table 1).

The maximal increase of resistance to the arrhythmogenic and general toxic effect of strophanthin was observed after combined injection of the μ-adrenoblocker anaprilin and the ganglioblocker pentamin. These data once again demonstrate the important role of adrenergic mediation of the heart in the pathogenesis of circulatory failure and in the mechanisms of development of cardiotoxic effects of glycoside cardiotonics [1,8,9]. Indeed, switch-off of the sympathetic innervation of the heart simultaneously at the ganglionic and postsynaptic (in the adrenergic synapses of the myocardium) levels by a combination of pentamine with anaprilin had a much better protective effect with respect to strophanthin cardiotoxicity than that brought about by a ganglioblocker or β-adrenoblocker alone. After administration of this drug combination the MAD and LD of strophanthin increased, respectively, by 114 and 75.4%, in acute cardiac insufficiency and by 116 and 70.1% in the subacute state. In intact animals this drug combination had a much weaker protective effect as regards strophanthin toxicity in comparison with the results of experiments with heart failure simulation.

Premedication with one β-adrenoblocker had a comparatively lower protective effect in both variants of cardiac insufficiency: after induction of the condition by both methods, glycoside cardiotonin MAD increased by 76.0% and LD by 18.8% in subacute and by 26.3% in acute heart failure. Pentamin switch-off of the sympathetic innervation of the heart at the level of the autonomic ganglia had a still weaker protective action vis-a-vis strophanthin toxicity in comparison with β-adrenoblocker effect, particularly so in cardiac failure induced by overexertion, when MAD showed just a tendency to increase

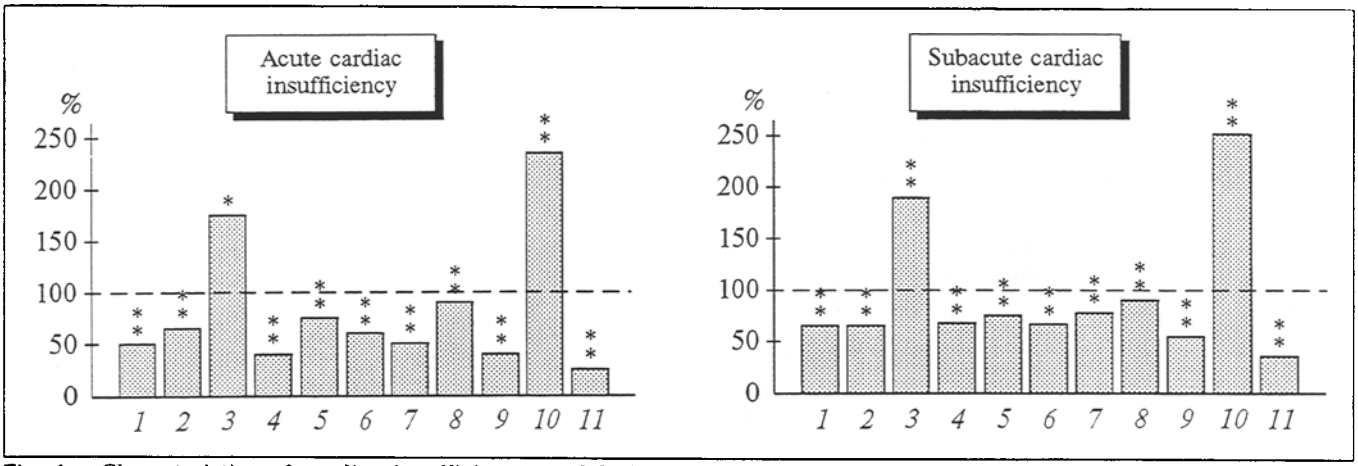

Fig. 1. Characteristics of cardiac insufficiency models in experimental rats. Abscissa: parameters of hemodynamics and electrolyte balance of the myocardium: *1*) minute blood volume; *2*) stroke volume; *3*) total peripheral vascular resistance; *4*) cardiac index; *5*) systolic index; *6*) left–ventricular work; *7*) left–ventricular work index; *8*) left–ventricular work stroke index; *9*) K^+ content in cardiomyocytes; *10*) Na^+ content in cardiomyocytes; *11*) K^+/Na^+ coefficient. Ordinate: values of the said parameters of hemodynamics and electrolyte balance of the myocardium in percent of their initial level. Dashed line (100%) shows the initial level of the parameters (control). One asterisk: $p<0.01$, two asterisks: $p<0.001$.

and LD increased by only 9.6%. This may be due to the incapacity of the ganglioblocker to eliminate the effects on the myocardium of humoral stress factors (of adrenalin, among others) released during exercise. Blocking of the autonomic ganglia in subacute cardiac insufficiency induced by isoprenaline impairment of the myocardium more markedly increased strophanthin tolerance: MAD increased by 22.0 and LD by 16.2%. At the same time in intact rats the β-adrenoblocker increased strophanthin tolerance to a lesser degree, whereas the ganglioblocker virtually did not change it.

Since heart failure is characterized not only by transmitter and electrolyte shifts in the myocardium, but also by impaired permeability of cell membranes [1,3], we thought it interesting to investigate the effect on strophanthin cardiotoxicity of a combination of the antiarrhythmic membrane stabilizer ajmaline, which shows a high protective efficacy in heart failure induced by both methods, and the ganglioblocker pentamin, which under conditions of left-ventricular insufficiency induces pharmacological relief of the lesser circulation. Premedication of experimental animals with a combination of pentamin and ajmaline led to a marked increase of tolerance of animals with cardiac insufficiency for strophanthin toxicity. Indeed, strophanthin MAD and LD in acute heart failure increased by 30 and 35% and in the subacute condition by 46 and 47.8%, respectively.

Combination of the peripheral vasodilator nitroglycerin, widely used in recent years in com-

TABLE 1. Effects of Some Drugs for Emergency Treatment of Heart Failure and their Combinations on Tolerance for Strophanthin Toxic Effect ($M \pm m$)

Drugs and their combinations	Experimental conditions					
	intact rats		acute CI		subacute CI	
	MAD	LD	MAD	LD	MAD	LD
Control	7.6±0.11	14.6±0.2	5.0±0.1	11.4±0.1	5.0±0.2	11.7±0.6
Anaprilin	11.7±0.2*	15.9±0.4*	8.8±0.3*	14.4±0.39*	8.8±0.3*	13.9±0.3*
Ajmaline	8.1±0.3	16.9±0.4*	10.2±0.4*	15.3±0.5*	10.3±0.4*	16.2±0.4*
Pentamin	7.7±0.2	14.7±0.2	5.5±0.3	12.5±0.4*	6.1±0.2*	13.6±0.3*
Nitroglycerin	7.2±0.3	14.2±0.3	5.3±0.3	11.5±0.4	5.1±0.1	10.8±0.4
Anaprilin + pentamin	10.7±0.4*	16.9±0.3*	10.7±0.5*	20.0±0.8*	10.8±0.4*	19.9±0.7*
Ajmaline + pentamin	8.5±0.4	16.7±0.3*	6.5±0.2*	15.4±0.3*	7.3±0.2*	17.3±0.3*
Anaprilin + nitroglycerin	8.3±0.3*	15.9±0.3*	8.5±0.3*	14.7±0.4*	7.6±0.3*	13.9±0.3*
Ajmaline + nitroglycerin	8.6±0.4	16.2±0.3*	6.3±0.1*	14.3±0.4*	8.5±0.3*	15.6±0.4*

Note. CI: cardiac insufficiency; asterisk: $p<0.05$ vs. corresponding control; MAD and LD in mg/kg.

bined drug therapy of circulation decompensation, with strophanthin had virtually no effect on tolerance for strophanthin toxicity in intact rats or in those with induced cardiac insufficiency, while preserving their hypersensitivity to the cardiotonin. At the same time, nitroglycerin combined with the β-adrenoblocker anaprilin or the membrane-stabilizer ajmaline brought about a pronounced protective effect vis-a-vis strophanthin toxicity in animals with cardiac insufficiency. In animals with acute heart failure premedication with a combination of anaprilin and nitroglycerin increased MAD and LD of glycoside cardiotonin by 70.0 and 28.9%, respectively, while in the subacute condition this drug combination increased MAD and LD by 52.0 and 18.7%, respectively. Combination of ajmaline with nitroglycerin increased the tolerance of experimental animals for the arrhythmogenic and general toxic effect of strophanthin by, respectively, 26.0 and 25.4% in acute heart failure and by 70.0 and 33.3% in the subacute condition. In intact rats the protective effect of these drug combinations was much lower, as was demonstrated by a lower increment of MAD and LD of glycoside cardiotonin in comparison with the results in animals with heart failure.

Hence, our findings demonstrate the possibility of recovery of tolerance for cardiac glycosides reduced in cardiac insufficiency by their combined administration with protectors from glycoside intoxication characterized by adrenonegative and membrane-stabilizing properties. Administration of the tested combinations of anaprilin and ajmaline with the ganglioblocker pentamin or the peripheral vasodilator nitroglycerin helps reduce the risk of glycoside intoxication under conditions of simulated cardiac insufficiency; thus, we recommend these drug combinations for clinical trials in cases with acute left-ventricular insufficiency associated with supraventricular disorders of the cardiac rhythm.

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