PHARMACOLOGY AND TOXICOLOGY

Comparative Evaluation of Pharmacological Effects of Combined Application of Strophanthin with Some Antiadrenergic Agents

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Pharmacological effects of strophanthin combined with the action of some antiadrenergic agents were studied on isolated frog atria and on models of acute and subacute cardiac insufficiency in rats. The studies demonstrated appreciable differences in the effects of anapriline, cordarone and tropaphen on strophanthin toxicity and on its chronoinotropic properties.

Key Words: *strophanthin; adrenergic agents; combined application*

Glycoside intoxication during pharmacotherapy of circulatory insufficiency (CI) presents a common problem for cardiologists [4], prompting the search for optimal modes of treatment and ways of preventing this serious complication. It has recently been demonstrated that hypersensitivity to toxic glycoside cardiotonics, which is typical for CI, can be successfully corrected by some therapeutics, antiadrenergic agents in particular [1,4]. However, the comparative efficacy of these preparations as pharmacoprotectors against glycoside intoxication and possible differences in their effects on other pharmacological properties of cardiac glycosides still remain unclear.

The purpose of the present study was compare the effects of anapriline, cordarone and tropaphen on strophanthin toxicity and on its chronoinotropic properties in CI models under various *in vivo* conditions and in isolated myocardial preparations *in vitro*.

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MATERIALS AND METHODS

Two hundred Wistar rats of body weight 160-260 g narcotized with sodium thiopental (40 mg/kg intraperitoneally) and 88 freshly isolated preparations of frog (*Rana ridibunda*) atria were used in the experiments. CI was induced in rats in two ways [5]: 1) physical overload caused by swimming till exhaustion, which induced acute CI; 2) a histotoxic effect of large doses of the β-adrenomimetic isoprenaline, which induced the development of subacute CI. Cardiac decompensation was documented by disturbances in the anatomy and histology of the internal organs typical for this kind of pathology, hemodynamics, and myocardial electrolyte balance, as well as by the appearance of hypersensitivity toward strophanthin. Tolerance for the glycoside cardiotonic was evaluated by biological titration of minimal arrhythmogenic (MAD) and lethal (LD) doses [2]. All antiadrenergic agents were administered 5 min prior to biological titration of cardiac glycoside MAD and LD to study the effect of anapriline (5 mg/kg), cordarone (5

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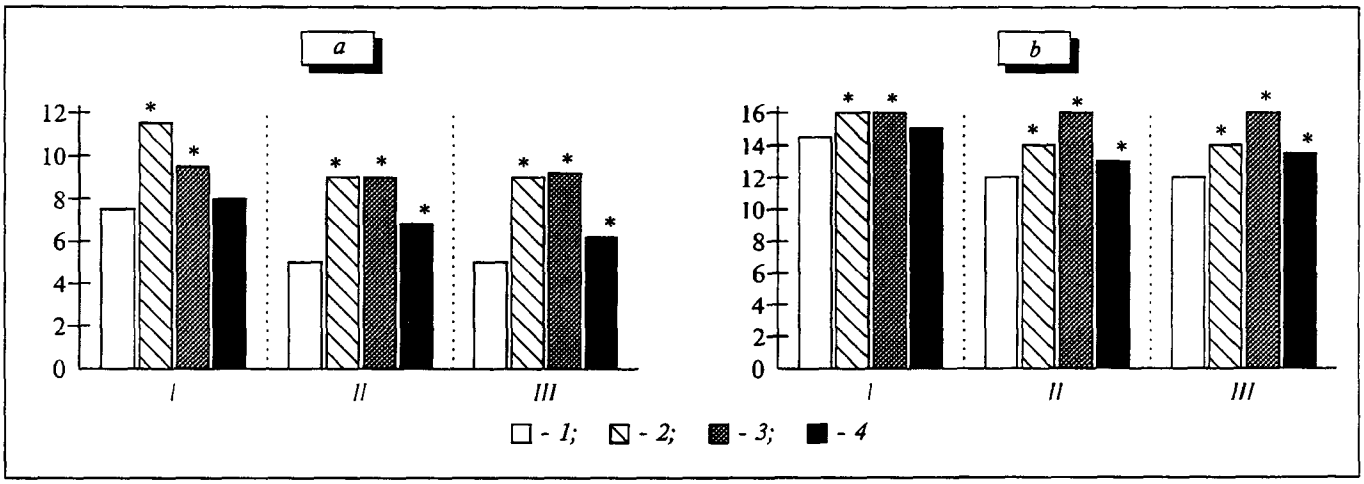

Fig. 1. Effect of anapriline, cordarone, and tropaphen on tolerance for the arrhythmogenic (*a*) and general toxic (*b*) action of strophanthin in intact rats (*I*) and in models of acute (*II*) and subacute (*III*) cardiac insufficiency. *1*) control; *2*, *3* and *4*) after premedication with anapriline, cordarone, and tropaphen, respectively. Ordinate: toxic doses of MAD (*a*) and LD (*b*) for strophanthin, mg/kg. Asterisk indicates significance of differences ($p<0.05$) from respective control.

mg/kg), and tropaphen (5 mg/kg) on strophanthin toxicity in intact rats and CI models. Experiments on isolated frog atria were performed to evaluate changes in the cardiotonic and chronotropic effects of strophanthin under the action of anapriline, cordarone, and tropaphen. The intensity and frequency of cardiac contractions were recorded in the isometric regime on a 6MX2B mechanotron [5]. A concentration of 10^{-3} g/liter was chosen as the "therapeutic" concentration which produced the maximum positive inotropic effect during a 10-min glycoside cardiotonic exposure.

The results of the experiments were processed by standard methods of variational statistics.

RESULTS

Figure 1 demonstrates that sensitivity toward the arrhythmogenic and general toxic effects of strophanthin was noticeably increased in the animals with induced CI, this being manifested in a decrease in MAD and LD of the glycoside cardiotonic by 34.3% and 19.9%, respectively, during subacute cardiac decompensation and by 34.3% and 22% during acute cardiac insufficiency. *In vivo* findings showed considerable differences in the effect of the antiadrenergic agents tested on strophanthin tolerance in intact rats and in different models of CI. Anapriline produced a pronounced protective effect with respect to the cardiotoxic action of strophanthin, raising its MAD by 76% irrespective of the type of CI. This β-adrenoblocker caused an 18.8% increase in LD during subacute cardiac decompensation and a 26.3% increase during acute cardiac insufficiency. Cordarone induced an 80% increase in MAD in the two CI models, and premedication with α-, β- and χ -blockers raised LD by 32.5% during subacute CI and by 38.6% during acute CI. Tropaphen, an α-adrenoblocker, exhibited a reliably weaker protective effect than anapriline and cordarone in the CI models with respect to strophanthin toxicity, raising MAD and LD by 34% and 20.2%, respectively, during acute CI and by 22% and 12.8% during subacute cardiac decompensation. On the other hand, premedication of healthy animals with α-adrenoblocker failed to protect against cardiac glycoside toxicity, while β-adrenoblocker and α-, β- and χ-blockers exhibited a considerably lower protective effect than in the CI models.

Table 1 shows that strophanthin exerts a two-phase effect on inotropic properties of the isolated myocardial streak *in vitro* against the background of progressive inhibition of the frequency of isometric contractions. The initially observed cardiotonic effect of cardiac glycoside was followed by a decrease in the contractile properties of the atrium as the time of treatment exposure increased. Anapriline, which exhibits an intrinsic property of producing negative chrono- and inotropic effects, in combination with strophanthin caused a shift to the right in the development of the positive inotropic effect of cardiotonic, inhibited the rate of its toxic manifestations, and potentiated the neagative chronotropic effect. Cordarone, in contrast to anapriline, inhibited contractions of the isolated myocardial streak to a much lesser extent, and the negative chronotropic effect of the preparation was accompanied by increased force of isometric contractions of the cardiac muscle. In combination with strophanthin, cordarone slightly slowed down the rate of progression of the positive inotropic

Table 1. Changes in Chronoinotropic Parameters of Isolated Myocardial Streak under the Effect of Strophanthin (10^{-3} g/liter) and Its Therapeutic Combinations with Anapriline (10^{-3} g/liter), Cordarone (5×10^{-3} g/liter), and Tropaphen (5×10^{-3} g/liter)

Preparations and combinations	Changes in parameters (%) from baseline level									
	1	2	3	4	5	6	7	8	9	10
Variations in amplitude of isometric contractions of myocardial streak										
Strophanthin	106.7±0.9*	118.3±1.8*	129.6±2.6*	138.5±2.3*	146.7±2.3*	128.7±6.5*	119.1±6.0*	109.3±5.5	104.8±6.3	98.6±6.0
Anapriline	96.4±1.0*	94.9±1.3*	92.1±1.5*	83.5±4.5*	77.4±4.9*	71.8±5.0*	65.7±6.1*	62.1±7.5*	58.7±6.8*	52.9±6.6*
Strophanthin + anapriline	102.3±3.3	105.6±5.1°	112.3±6.9°	116.6±7.4*°	124.9±8.8*°	126.9±6.2*	123.9±6.0*	117.5±6.7*	111.4±6.8	106.5±7.2
Cordarone	99.5±1.5	101.1±1.9	100.9±1.8	101.7±2.4	104.0±2.2	106.4±2.2*	109.1±2.9*	112.5±3.6*	115.2±2.8*	117.4±1.8*
Strophanthin + cordarone	101.4±2.3°	108.8±3.2*°	121.3±4.8*°	132.7±5.9*	139.7±6.5*	143.5±8.5*	141.3±8.6*°	140.7±7.9*°	135.7±7.3*°	130.1±5.1*°
Tropaphen	96.1±2.5	94.4±2.4*	92.3±2.4*	91.2±2.9*	90.9±3.2*	91.3±3.5*	89.7±3.8*	90.1±4.4*	89.9±4.5*	89.0±3.7*
Strophanthin + tropaphen	104.4±3.4	110.0±5.0*	120.0±5.7*	126.3±7.2*	134.5±6.9*	131.8±7.1*	125.9±6.6*	117.8±4.7*	113.2±4.3*	104.0±4.5
Variations in frequency of isometric contractions of myocardial streak										
Strophanthin	99.0±0.6	97.0±1.5*	94.8±2.1*	92.0±2.3*	82.6±3.0*	74.6±4.2*	71.7±4.7*	69.3±4.6*	69.3±4.6*	67.7±5.2*
Anapriline	100.0±0.0	98.9±1.0	97.4±1.9	94.4±3.3	91.9±3.6*	81.9±4.2*	75.7±3.0*	66.1±4.4*	65.0±5.1*	62.1±4.2*
Strophanthin + anapriline	91.8±6.1	86.0±6.5*	81.5±8.3*	76.5±9.2*	71.7±7.8*	69.8±6.8*	64.7±6.8*	57.7±6.4*	54.3±4.8*°	51.0±3.9*°
Cordarone	100.0±0.0	98.8±1.1	97.5±1.9	96.2±2.1	95.0±2.8	93.7±2.4*	92.2±2.9*	90.5±2.3*	89.8±2.3*	88.3±2.5*
Strophanthin + cordarone	100.0±0.0	98.3±1.6	97.0±2.2	95.7±2.4	94.3±2.1*°	92.8±1.3*°	91.3±1.9*°	89.8±2.6*°	87.8±1.8*°	86.3±2.1*°
Tropaphen	100.0±0.0	98.5±1.2	96.9±2.6	95.4±3.3	94.1±3.5	92.9±4.2	89.1±5.2*	87.6±5.9*	85.5±5.2*	84.3±5.6*
Strophanthin + tropaphen	98.6±1.3	97.1±2.4	92.9±4.2	89.4±3.2*	83.0±2.5*	76.9±3.0*	69.3±4.1*	66.4±3.8*	65.0±4.4*	63.3±3.4*

Note: Asterisk indicates significance of differences compared to the baseline (100%) level, circle – compared to the effect of strophanthin.

effect of cardiac glycoside, at the same time greatly prolonging its effect and preventing the appearance of any toxic symptoms. In addition, cordarone slightly attenuated the negative chronotropic effect of strophanthin. The α-adrenoblocker, tropaphen, which exhibits weak negative chrono- and inotropic effects, brought about no significant changes in the cardiotonic and bradycardiac effects of cardiac glycoside when combined with it.

Our findings testify to a marked protective effect of the antiadrenergic agents tested with respect to strophanthin cardiotoxicity in modeled CI, the β-adrenoblocking drugs being more active. This can be considered as additional evidence for the prevalence of β-adrenoreceptors in the myocardium, which are currently believed [1,4] to participate in the realization of the toxic effects of glycoside cardiotonics. This probably accounts for the less pronounced negative chronoinotropic effects of the α-adrenoblocker tropaphen than the β-adrenoblocker anapriline. β-Adrenonegative agents correct lowered tolerance for strophanthin toxicity by blocking the enhanced sympathetic effects on the heart arising due to the mobilization of the sympathetic-adrenal system as a CI compensation factor. The intrinsic property of anapriline of inhibiting free-radical lipid peroxidation probably plays a certain role in the prevention of toxic effects of cardiac glycoside [6]. Some of the effects of catecholamines are apparently mediated via α-adrenoreceptors under conditions of circulatory insufficiency. In fact, the activation of the sympathetic-adrenal system observed in this pathology may lead to excessive vasoconstriction [9], which in turn promote the development of hypoxia, acidosis, and release of biologically active substances which potentiate glycoside cardiotonic toxicity [1]. This may be the reason that tropaphen failed to produce a protective effect in the absence of sympathetic vasoconstriction (in intact animals), whereas in the CI models this preparation demonstrated a pronounced ability to prevent the development of strophanthin toxicity. It is of interest to note that cordarone, which blocks both β- and α-adrenoreceptors, appears to better protect the myocardium from increased adrenergic effects and therefore even slightly surpasses anapriline in its

protective efficacy, not to mention tropaphen, which selectively turns off some adrenoreceptors. A marked protective effect of cordarone with respect to strophanthin toxicity is observed despite its intrinsic ability to induce an elevation in the concentration of glycoside cardiotonics in the plasma [8]. Cordarone is also known [3,7] to limit Na^+, as well as to some extent Ca^{2+} inflow into cardiomyocytes. Furthermore, the preparation inhibits K^+ penetration via cell membranes, i.e., its effect on transmembrane ion transport is opposite to that of cardiac glycosides. This evidently explains the less pronounced negative chronotropic effect of strophanthin caused by α-, β- and χ-blockers.

Thus, models of acute and subacute CI, as well as experiments on isolated myocardial preparations showed substantial differences in the effect of the studied antiadrenergic agents on the main pharmacological effects of strophanthin, which must be taken into consideration during combined application of preparations of these groups for pharmacotherapy of cardiac decompensation in order to increase its efficacy and safety.

Experiments on two CI models in rats demonstrated different efficacies of anapriline, cordarone, and tropaphen as protectors against glycoside intoxication.

Anapriline in combination with strophanthin potentiated its negative chronotropic effect in isolated myocardial preparations and slightly diminished its cardiostimulating effect, slowing the rate of its development. Cordarone in combination with cardiac glycoside lessened its negative chronotropic effect and caused a shift to the right in the development of the cardiotonic effect. No significant changes in chrono- and inotropic effects of glycoside cardiotonic were observed with tropaphen.

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