PHARMACOLOGY

Effects of the Membrane Stabilizer Ajmaline and the Local Anesthetic Trimecaine on the Pharmacological Effects of Strophanthin *in Vivo* and *in Vitro*

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Under conditions of simulated circulation failure in rats ajmaline increases tolerance for strophanthin cardiotoxicity to a greater extent than trimecaine. In isolated preparations of frog myocardium both antiarrhythmic agents somewhat weaken the inotropic effect of the cardiac glycoside and virtually do not influence its chronotropic effect.

Key Words: *strophanthin cardiotoxicity; ajmaline; trimecaine*

Frequently developing glycoside intoxication is one of the side effects of cardiac glycosides used in drug therapy of circulation failure (CF), necessitating a search for measures to prevent this side effect. Recently the possibility of drug correction of hypersensitivity to cardiac glycoside cardiotoxicity typical in circulation failure has been confirmed experimentally and clinically [2,5]. But it is still unknown how the use of drugs protecting against glycoside intoxication may reflect the cardiotonic effect of cardiac glycosides.

The aim of the present investigation was to study the effects of the membrane stabilizer ajmaline and the local anesthetic trimecaine, which are frequently prescribed together with cardiac glycosides, on the basic pharmacological properties of strophanthin *in vivo* and *in vitro*.

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MATERIALS AND METHODS

Experiments were carried out on 180 Wistar rats weighing 160 to 260 g narcotized with sodium thiopental (40 mg/kg intraperitoneally) and on 83 fresh preparations of atria of *Rana ridibunda*.

Circulation failure was induced in the rats by two methods [3]: a maximally tolerable swimming load to the point of complete exhaustion, leading to the development of acute circulation failure, or histotoxic exposure of the myocardium to high doses of isoprenaline, a β-adrenomimetic inducing subacute circulation failure. The presence of circulation failure in the animals was confirmed by the detection of hemodynamic disorders typical of this condition, the anatomical and histological picture of the viscera, shifts in the myocardial electrolytic balance, and changed tolerance for the arrhythmogenic and general toxic effects of strophanthin; this latter characteristic was assessed by biological titration of the minimal arrhythmogenic and lethal doses (MAD and LD) of the cardiotonic [3]. For

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TABLE 1. Effects of Ajmaline and Trimecaine on Tolerance for Arhythmogenic and General Toxic Effects of Strophanthin in Intact Rats and in Rats with Induced Circulaion Failure (mean±SEM)

Strophanthin dose	Experimental conditions		
	intact rats	acute CF	subacute CF
	Control		
MAD	7.6±0.11	5.0±0.10 $p<0.001$	5.0±0.22 $p<0.001$
LD	14.6±0.20	11.4±0.14 $p<0.001$	11.7±0.58 $p<0.001$
	After ajmaline premedication MAD LD		
MAD	8.1±0.26	10.2±0.40 $p_{1,2}<0.001$	10.3±0.42 $p_{1,2}<0.001$
LD	16.9±0.42 $p_{1,2}<0.001$	15.3±0.46 $p_{1,2}<0.001$	16.2±0.36 $p_{1,2}<0.001$
	After trimecaine premedication		
MAD	6.2±0.26 $p_{1,3}<0.001$	6.0±0.24 $p_{1,3}<0.001$	5.5±0.22
LD	13.5±0.49 $p_{1,3}<0.05$	12.6±0.40 $p_{1,3}<0.01$	11.9±0.34

a study of the effects of antiarrhythmic drugs on strophanthin toxicity ajmaline in a dose of 5 mg/kg and trimecaine in a dose of 15 mg/kg were i.v. injected 5 min before titration of MAD and LD of cardiac glycosides. Changes in the cardiotonic and chronotropic effects of strophanthin under the influence of ajmaline and trimecaine were studied *in vitro* in isolated frog atria. The force and frequency of myocardial contractions were recorded in an isometric mode using a 6MKh2B mechanotron [1]. A strophanthin concentration of 10^{-3} g/liter was selected as "therapeutic" in a cuvette; in our experiments this concentration had the maximal positive inotropic effect during a 10-min exposure to the glycoside cardiotonic. "Therapeutic" concentrations of ajmaline and trimecaine were, respectively, 5×10^{-3} and 1.5×10^{-2} g/liter, that is, *in vitro* the same ratios of "therapeutic" concentrations of the drugs were taken as *in vivo*. The results were processed by routine methods of variational statistics [6].

RESULTS

The data on the effects of antiarrhythmic drugs on strophanthin toxicity are summarized in Table 1, which shows that ajmaline and trimecaine influenced the experimental animals' tolerance for cardiac glycosides differently. The membrane stabilizer ajmaline, no matter by which method circulatory failure was induced, drastically increased tolerance for the cardiotoxic effect of strophanthin, increasing its MAD more than twofold. The LD of the glycoside cardiotonic rose by 34.2% in acute circulatory failure and by 38.5% in the subacute condition. In comparison with ajmaline, premedication with the local anesthetic trimecaine much less intensively increased the resistance of the animals to the toxic effect of strophanthin, particularly so in subacute circulation insufficiency, when there was just a tendency toward an increase of the MAD and LD of the cardiotonic. The protector effect of trimecaine was more marked in acute circulation failure: MAD rose by 20% and LD by 10.5%.

The results of our studies of the effect of ajmaline and trimecaine on the tolerance of strophanthin in intact animals differ considerably from the data obtained in experimental rats with induced circulatory failure. The membrane stabilizer and local anesthetic in these experiments had different effects on the resistance of healthy rats to strophanthin. Whereas ajmaline had a tendency to increase the cardiac glycoside's MAD and reliably (by 15.8%) increased its LD, trimecaine, on the contrary, decreased tolerance of the glycoside cardiotonic, reducing its MAD and LD by 18.4 and 7.5%, respectively.

Such different effects of the tested antiarrhythmic agents on the tolerance for strophanthin toxicity may be connected with specificities of their mechanisms of action. Like quinidine, ajmaline is known to inhibit the transmembrane Na^+ flow in myocardial cells and their release of K^+, this naturally increasing the cardiac muscle tolerance for the toxic effect of strophanthin [7]. The protector effect of ajmaline is to a certain extent determined by its own sympatholytic properties [8]. In contrast to ajmaline, trimecaine has only a negligible influence on the rapid Na^+ flow into cardiomyocytes but facilitates K^+ release by them [4], which seems to aggravate the hypokalihistia observed in

circulation failure. For this reason, in the case of circulatory insufficiency administering the membrane stabilizer ajmaline to treat glycoside intoxication seems to be more advisable than using trimecaine, an antiarrhythmic drug belonging to the group of local anesthetics. The detected differences in the effects of antiarrhythmic drugs on the strophanthin tolerance of intact animals and animals with circulation failure point clearly to the role of impaired permeability of cell membranes in circulatory failure as one of the major risk factors of glycoside intoxication.

Of course, combined therapy with ajmaline and trimecaine together with cardiac glycosides does not rule out the possibility of a certain attenuation of the positive inotropic effect of the latter agent. We therefore investigated the effects of each antiarrhythmic agent separately and in combination with the glycoside cardiotonic on the force and frequency of contractions of an isolated frog atrium. The results presented in Table 2 demonstrate that during a 10-min exposure in a cuvette, strophanthin had a biphasic effect on the amplitude of isometric contractions of a myocardial strip. The initially observed cardiotonic effect of the glycoside then gave way to its marked attenuation, and just 8 min after the start of the experiment atrial contractility was virtually the same as initially. Our results, no doubt, experimentally confirm the hypothesis put forward by many scientists on the biphasic nature of the response of cardiac glycosides [9,10]. Moreover, experiments with isolated heart preparations revealed a negative chronotropic effect of strophanthin, this possibly being further evidence of a direct inhibitory effect of cardiac glycosides on the sinus node.

The antiarrhythmic membrane stabilizer ajmaline, which rather weakly depressed the contractility of an isolated myocardial strip in the course of exposure, nevertheless induced a marked progressive inhibition of the frequency of its contractions. In combination with strophanthin ajmaline markedly depressed the cardiostimulating effect of the glycoside during the first 5 min of exposure and virtually did not influence its chronotropic effect. Trimecaine, which did not in itself change the chronotropic properties of an isolated myocardial strip and only negligibly influenced the myocardial chronotropic parameters, when combined with strophanthin displayed a clear-cut negative influence on the cardiotonic effect of cardiac glycosides as soon as during the first 5 min of ex-

TABLE 2. Effects of "Therapeutic" Concentrations of Strophanthin, Ajmaline, Trimecaine, and Their Combinations with a Cardiac Glycoside on Chronotropic Parameters of the Myocardium (mean±SEM)

Exposure, min	Changes in parameter after drug administration, % of initial level				
	strophanthin	ajmaline	strophanthin + ajmaline	trimecaine	strophanthin + trimecaine
	Changes in amplitude of myocardial isometric contractions				
1	106.7±0.09*	99.5±1.0	101.8±1.7°	100.5±1.2	100.7±2.0°
2	118.3±1.8*	98.3±1.3	105.6±1.8°°	100.4±1.8	102.4±2.8°
3	129.6±2.6*	96.4±2.00	108.9±2.5°°	96.4±2.9	107.7±2.6°°
4	138.5±2.3*	94.7±2.7*	111.2±4.3°°	95.0±3.9	110.1±3.7°°
5	146.7±2.3*	95.4±2.7	120.1±5.6°°	93.4±3.9	113.5±3.8°°
6	128.7±6.5*	94.9±2.9	121.8±6.7*	91.6±4.1*	113.2±5.4*
7	119.1±6.0*	93.1±3.7	111.2±4.4*	92.0±3.5*	113.3±6.8*
8	109.3±5.5	92.5±3.6*	101.8±3.7	93.1±2.9*	107.6±6.4
9	104.8±6.3	91.2±4.3*	101.0±2.5	94.7±3.4	104.6±6.2
10	98.6±6.0	90.8±4.3*	97.7±4.0	95.5±3.1	99.1±9.2
	Changes in frequency of myocardial contractions				
1	99.0±0.6	98.8±0.7	98.8±1.0	100.0±0.0	96.7±3.1
2	97.0±1.5*	96.3±1.4*	96.3±2.7	100.0±0.0	93.8±4.6
3	94.8±2.1*	92.9±1.8*	92.6±3.5*	99.7±1.7	92.2±5.9
4	92.0±2.3*	90.3±2.5*	90.5±3.4*	99.7±1.7	90.5±7.1
5	82.6±3.0*	84.8±3.0*	80.8±2.5*	99.7±1.7	84.3±5.9*
6	74.6±4.2*	80.0±3.5*	73.5±3.0*	99.3±3.6	78.0±7.3*
7	71.7±4.7*	74.9±3.6*	69.1±4.9*	97.9±3.3	73.0±5.4*
8	69.3±4.6*	69.8±3.0*	66.4±4.1*	97.9±3.3	71.3±5.0*
9	69.3±4.6*	65.7±2.7*	64.4±3.1*	97.9±3.3	68.5±6.9*
10	67.7±5.2*	61.4±2.9*	61.9±2.3*	97.9±3.3	65.8±5.9*

Note. Asterisk: reliable differences vs. initial level (100%) before drug administration; circle: reliable shifts vs. strophanthin effect.

posure, and this was not attended by a marked alteration of its chronotropic effect.

Hence, the data of our experiments on the simulation of acute and subacute circulatory failure and in isolated myocardial preparations indicate certain differences in the effects of antiarrhythmic drugs with different mechanisms of action on the toxic, cardiotonic, and chronotropic effects of strophanthin. In contrast to trimecaine, ajmaline greatly increased the resistance of a weak heart to strophanthin cardiotoxicity under conditions of simulated circulatory failure. On the other hand, both antiarrhythmic agents somewhat attenuated the cardiotonic effect of cardiac glycosides, and this should be borne in mind when prescribing combinations of these drugs. Evidently, clinical use of ajmaline in combination with cardiac glycosides is preferable to combinations with trimecaine, particularly so if manifest symptoms of the toxic effects of glycoside cardiotonics are to be eliminated.

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MICROBIOLOGY AND IMMUNOLOGY

The "Familial" Factor and the Microbiocenosis of the Normal Human Intestine

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Population genetics methods are used to study the relationship between living in the same environment and the formation of the large-intestine microflora in healthy persons. The variability of a microbiological phenotype is found to depend mainly on random factors and is virtually unrelated to the "familial" constituent.

Key Words: *familial analysis; normal microflora*

It is well known that people in close communal contact are frequently characterized by a certain similarity of the large-intestine microflora. It could hardly be disputed that this regularity is to a great extent explained by shared living conditions, primarily of a social nature. Nevertheless, this a

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