EFFECT OF SOME ADRENERGIC AGENTS ON THE CUMULATIVE EFFECT OF STROPHANTHIN

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The effect of pharmacological blockade and stimulation of the adrenergic innervation on the toxicity and cumulative effect of strophanthin was studied in experiments on cats. Premedication with propranolol and preliminary reserpinization were found to increase tolerance to strophanthin and to weaken its cumulative effect. Isoprenaline sharply increased sensitivity to the cardiac glycoside, but in this case cumulation was totally absent.

KEY WORDS: *strophanthin; adrenergic mechanisms; heart.*

Previous investigations showed that the adrenergic component participates in the mechanism of the inotropic and arrhythmia-producing effect of strophanthin and also influences the level of its toxicity [3, 4, 6-8, 11].

It was decided to study the degree to which pharmacological blockade and stimulation of the adrenergic innervation may be reflected in the cumulative effect of strophanthin.

EXPERIMENTAL METHOD

The toxicity and cumulative effect of strophanthin G (ouabain) were studied in 59 cats weighing 1.8-2.8 g, anesthetized with pentobarbital sodium (30 mg/kg) and with differences in the state of their adrenergic innervation. Toxicity was assessed as the minimal lethal dose of strophanthin when injected intravenously in a concentration of 8×10^{-6} at the rate of 1 ml/min until cardiac arrest.

To determine the cumulative effect of strophanthin, the glycoside was injected intramuscularly into the animals daily for 5 days in a dose equivalent to 7% of the minimal lethal dose. On the 6th day the lethal dose of strophanthin was determined for these animals. The presence of significant differences between the minimal lethal dose of the glycoside, reflecting its initial toxicity, and the lethal dose established for animals receiving the glycoside repeatedly, indicated an increase in sensitivity to strophanthin as a result of its cumulative action.

The toxicity and cumulative effect of strophanthin were determined in four series of experiments: on intact animals (control), after administration of the β-adrenolytic propanolol (Inderal) injected intramuscularly in a dose of 4 mg/kg 5 min before each injection of the glycoside, after administration of reserpine (intramuscularly, 1 mg/kg, 24 h before the first injection of strophanthin and 24 h before determination of the lethal dose of the glycoside), and after administration of the β-adrenomimetic isoprenaline (injected intramuscularly in a dose of 8 mg/kg 5 min before each dose of the glycoside).

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TABLE 1. Cumulative Effect of Strophanthin after Administration of Antiadrenergic Drugs and Adrenomimetics

Experiment conditions	Dose of drug (in mg/kg)	Number of experiments	Lethal dose of strophathin (in μg/kg)	
			for animals not receiving glycoside	after 5th dose of glycoside
Control				
toxicity	—	9	125±4,7	—
cumulation	—	5	—	78±6,5
After administration of propranolol				
toxicity	4	11	166±8,0	—
cumulation	4	6	—	132±10,6
After administration of reserpine				
toxicity	2	6	185±10,8	—
cumulation	2	6	—	169±12,7
After administration of isoprenaline				
toxicity	8	10	82±4,9	—
cumulation	8	6	—	90±7,1

EXPERIMENTAL RESULTS AND DISCUSSION

Blocking the adrenergic innervation of the heart by propranolol and preliminary injection of the sympatholytic reserpine significantly increased tolerance to strophanthin. Stimulation of the β-adrenoceptors of the myocardium by isoprenaline, on the other hand, appreciably increased the sensitivity of the animals to the cardiac glycoside (Table 1).

In the control experiments daily administration of strophanthin to the cat in a dose equivalent to 7% of the minimal lethal dose had a marked cumulative effect. These animals died after a significantly ($P < 0.05$) smaller dose of the cardiac glycoside. Similar results on the cumulative action of strophanthin and its analogues (Corglycon, Convallaria majalis glycosides) were obtained previously [2, 5].

Premedication with propranolol before each injection of the glycoside (given in a dose of 7% of the minimal lethal dose when given in conjunction with propranolol) substantially weakened the cumulative effect of strophanthin. Repeated injection of strophanthin after preliminary reserpinization virtually did not cause cumulation.

The adrenolytic and sympatholytic drugs thus not only increased tolerance to strophanthin, but also weakened its cumulative action.

Pharmacological stimulation of the β-adrenoceptors with isoprenaline led to an ambiguous result: sensitivity to the glycoside was considerably increased but the cumulative action during repeated administration of strophanthin was totally absent.

In the modern view [1, 9, 10] cumulation of cardiac glycosides is due to the character of their metabolic transformation in the liver and intestine. The adrenergic component evidently plays a role in the regulation of these processes and can modify the degree of cumulative action of the cardiac glycosides.

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