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ON THE REACTIVITY OF THE ORGANISM TO CARDIAC GLUCOSIDES IN THEIR COMBINED USE WITH ANTICOAGULANTS

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Chair of Pharmacology (Head -- Prof. M. M. Nikolayeva) of Moscow Pharmaceutical Institute.

The anticoagulants dicoumarin and neodicoumarin which had entered into medical use in recent years have been described in the literature mainly from the point of view of their effect on the process of blood coagulation. Other facets of their pharmacological action have been little studied.

There has been virtually no work done on the problem of the combined use of anticoagulants with other medicinal preparations, in particular with the cardiac glucoside preparations as encountered under clinical conditions. The need for it is dictated, on the one hand, by the fact that weakness of cardiac activity originating in myocardial infarcts represents an indication for the administration of cardiac glucosides and, on the other hand, according to numerous observations in cardiovascular diseases, thromboembolic complications are encountered quite frequently, especially in rheumatic cardiac valvular diseases. According to reported data, infarcts of the spleen, kidneys and lungs are observed in 30 to 66 percent of patients with various cardiovascular diseases (N. Z. Abrosimov, etc.).

In analyzing the origin of such complications, great significance is now being attached to the factors which affect the process of blood coagulation, among them the medicinal substances widely used in certain diseases. Of these, the digitalis preparations considered by many authors as capable of increasing blood coagulability are attracting special attention (A. Z. Davletkil'deyeva and coauthors,

L. P. Buyko, N. Z. Abrosimov, Macht, Supek, Pere, etc..). In order to reduce the frequency of thromboembolic complications and to effect a more favorable course of already present complications, the clinicians recommend simultaneous administration of cardiac glucosides and anticoagulants (Ye. M. Tareyev, L. P. Buyko, R. I. Averina, Peters, Guyther, Brambel, etc.).

However, the problem of the combined effect of cardiac glucosides and anticoagulants up to now has not as yet been subjected to special experimental study. There is only a report by Macht relating to this problem. This scientist employed heparin (to reduce the coagulability of blood) in his experiments on the biological evaluation of cardiac glucosides) and noted that under such experimental conditions, the lethal dose of digitalis and strophanthin was higher.

In the present work we submitted the results of our experiments on the study of the effect of dicoumarin on the resistance of animals to digitalis, strophanthin and adoniside.

Experiments were carried out on 120 frogs and also on cats, according to the method described in the State Pharmacopeia, eighth edition for the biological evaluation of cardiac glucosides. Dicoumarin was administered internally every other day in a 400 microgram dose per frog for a period of seven days, or in a single administration. The control animals were kept under similar conditions for the same period of time.

After that, the experimental and control frogs received in various doses the standard digitalis preparation in a 1:4 dilution (Table 1).

A dose of 0.3 ml caused cessation of the heart beat in four out of five animals within 40 to 52 minutes.

In the experiments with dicoumarin, considerably higher doses of digitalis were required to achieve the same effect. Thus, for example, even a 0.45 ml was insufficient to effect a systolic arrest of the heart in the majority of frogs. In these series of experiments the indicated effect was present only in two out of five animals; at that, in one of them it was only temporary -- after 66 minutes the heart stopped in the state of diastole.

Thus, on the basis of obtained results one can arrive at the conclusion that a preliminary repeated administration of dicoumarin increases the resistance of frogs to digitalis, as a result of which the minimal toxic dose causing a systolic arrest of the heart is increased approximately by 30 percent, as compared to control.

Table 1

Effect of dicoumarin on the resistance of frogs to digitalis (dilution of the standard preparation is 1:4)

Number of frogs	Digitalis does in ml	Systolic stoppage of heart: Time following administration in minutes	Systolic stoppage of heart: Percent in proportion to the total number of frogs	Annotation
		Experiment		
4	0.5	30;26;26;31	100	In one frog the heart stopped in a systole, then resumed contraction and finally stopped in diastole.
5	0.45	33; 50	40	
5	0.4	45; 47	40	In one frog heart activity was resumed
		Control		In one frog toxic signs
3	0.45	23;32;44	100	
5	0.4	30;34;46	80	
5	0.3	28;40;52;52	80	

In experiments with adonisid, conducted under the above-mentioned conditions, analogous results were obtained. In controls the minimal dose of adonisid in 1:8 dilution was 0.3 ml, whereas in frogs who had been given dicoumarin, the arrest of the heart after 0.4 ml occurred only in 50 percent of cases.

In studying the reactivity of frogs to strophanthin, we administered dicoumarin to the animals once, three days prior to the critical experiment. But even in a single administration of dicoumarin one could note the increase of frogs' resistance to strophanthin, since the arrest of the heart occurred in these animals following a larger dose of the preparation and at later periods.

Thus, in three series of experiments with various cardiac glucosides analogous results were obtained, attesting to the fact that against the background of dicoumarin the resistance of frogs to cardiac glucosides increases.

We must note that in the experiments with preliminary administration of dicoumarin we observed the predominance of the diastolic effect over the systolic following the action of cardiac glucosides.

Table 2

Effect of dicoumarin on the resistance of cats to strophanthin

Weight of animal in grams	Lethal dose of strophanthin in mg/kg	Changes in percentages as compared to control
	Experiment	
2400	0.129	+18.3
2600	0.253	+133
3800	0.145	+33
3550	0.080	—27
3300	0.101	—7.3
2700	0.122	+11.9
2250	0.140	+28.4
Average	0.139	+27.5
	Control	
2300	0.106	
2500	0.108	
3500	0.124	
3600	0.100	
Average	0.109	

In order to confirm this observation, we conducted experiments on an isolated heart of a frog. In a simultaneous perfusion of the heart with a 1: 20,000 solution of stophanthin and a 1: 1,000,000 concentration of dicoumarin a more pronounced diastolic affect was elicited as compared to control experiments. The cardiac arrest took place in the diastole.

In experiments on cats the combined effect of dicoumarin and strophanthin was investigated. The first preparation was administered internally daily for four days at 50 to 60 mg per animal. On the fifth day the infusion of a 1: 150,000 solution of strophanthin was administered at the rate of one ml per minute. An hour prior to the infusion, the cats were injected subcutaneously with 0.25 gm per kg of medinal per animal (Table 2).

The average dose causing a cardiac arrest in the animals consisted of 0.139 mg per kg, and in control animals -- 0.109 mg per kg.

Thus, as in the experiments on frogs, the cardiac arrest required a larger quantity of strophanthin (by 27.5 percent).

In analyzing the results of various experiments our attention is attracted to the considerable divergence in the amounts of lethal doses -- a fact possibly connected with the individual reaction of the animals to dicoumarin administration. An individual reaction to the use of anticoagulants was also observed in their effect on patients in therapeutic doses.

Conclusions

1. Experiments conducted on frogs and cats demonstrated that the reactivity of the organism in respect to cardiac glucosides changes against the background of the action of dicoumarin.

2. The resistance of frogs to digitalis, adonisid, and strophanthin against the background of dicoumarin action is considerably increased.

3. In experiments on an isolated heart of a frog in its simultaneous perfusion with a strophanthin and dicoumarin solution, an arrest of the heart in diastole takes place, and in perfusion with strophanthin only -- in a systole.

4. The resistance of cats to strophanthin against the background of dicoumarin action increases in the majority of cases.

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