

PHARMACOLOGY

THE EFFECT OF PAPAVERINE AND DIBAZOL* ON THE RATE OF THE CORONARY CIRCULATION

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The drugs used in the treatment of angina pectoris exert different effects on the coronary vessels. In this respect their comparative experimental evaluation is of great interest. We began the study of the drugs used in the treatment of coronary insufficiency with an investigation of papaverine and dibazol.

The effect of papaverine on the coronary vessels was studied experimentally at first on the isolated heart [5, 7, 10], and later on the heart-lung preparation [8] and on the heart in situ [3, 4, 9]. However, no detailed investigation of the effect of papaverine on the coronary vessels of the intact animals has yet been made.

Despite the clinical use of dibazol there is insufficient experimental confirmation of its effect on the coronary vessels. The references in the literature to this problem are confined to the work of D. S. Paskov [2], who showed that dibazol causes slight dilation of the lumens of the coronary vessels of the isolated human heart. Generally speaking no investigation of the effect of dibazol on the coronary vessels has been carried out in the intact animal. Similarly no study has been made of the combined effect of papaverine and dibazol on the rate of the venous blood flow. Nevertheless a combination of the two drugs is often used in clinical practice.

EXPERIMENTAL METHOD

In this work we used a method which permitted determination of the rate of flow of a volume of blood from the coronary sinus. The experiments were performed on cats under nembutal anesthesia (40 mg/kg). With the application of artificial respiration to the animals, the thorax was opened and a polythene catheter introduced into the coronary sinus through the right auricle, after which heparin was injected (1500 units/kg body weight of the animal). The blood from the coronary sinus passed along the polythene catheter into a measuring tube and caused a small float to rise, the movement of which was recorded mechanically on the smoked drum of a kymograph. The volume of blood flowing from the coronary sinus in 15 min was measured periodically. A detailed account of the method was given in the paper by N. V. Kaverina [1].

The size of the blood flow was estimated in ml/min per 100 g weight of the heart. Normally the mean volume of blood flowing from the coronary sinus of the cat amounted to 43 ml/min per 100 g weight of the heart (results of 35 experiments) with a mean square deviation of 13.8. This value of the rate of the blood flow in the heart corresponds approximately to the figures obtained by Gregg in experiments on dogs.

The blood pressure in the carotid artery was recorded. The tested drugs were injected intravenously.

* Dibazol is 2-benzyl-benzimidazol hydrochloride — Publisher's note.

EXPERIMENTAL RESULTS

Experiments with Papaverine

The character of the effect of papaverine on the rate of the coronary blood flow may be judged from Fig. 1: in an effective dose (2 mg/kg) papaverine causes a marked increase in the rate of the blood flow from the coronary sinus.

TABLE 1

The Effect of Papaverine and Dibazol on the Rate of the Coronary Blood Flow

Drug	Dose in mg/kg	No. of expts.	Maximum increase in rate of coronary blood flow in %		Duration of action in minutes	
			mean values	limiting values	mean values	limiting values
Papaverine	0.5	10	28	10 & 70	10	3 & 15
	1	6	44	26 & 55	12	3 & 40
	2	6	72	38 & 116	45	20 & 55
	4	1	114	—	1 hr 30 min	—
Dibazol	3	5	18	10 & 24	Duration of action was 2-3 min irrespective of dose. It reached 10 min in only one experiment.	
	5	6	30	15 & 43		
	10	5	39	33 & 60		
	20	1	10	—		

The summarized results of the series of experiments with papaverine are shown in Table 1. With increase in the dose of papaverine the strength and duration of its action increased. In a dose of 0.5 mg/kg papaverine causes maximum increase in the rate of the coronary blood flow by 28% for 10 min; in a dose of 4 mg/kg, in spite of a sharp fall in blood pressure, it increases the rate of the blood flow by 114% and its action lasts 1.5 hrs.

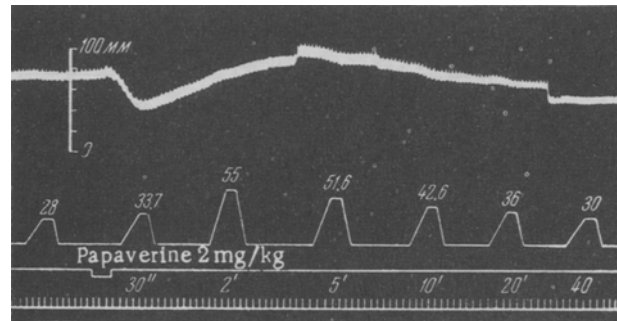


Fig. 1. The effect of papaverine on the rate of the blood flow from the coronary sinus. Interpretation of the curves (from above downwards): arterial pressure, blood flow from the coronary sinus, stimulation marker, time marker (5 sec). The figures indicate rate of flow of blood in ml/min per 100 g weight of the heart. The figures below the line of the time marker indicate the length of time after the injection of the drug that determination of the rate of the blood flow was made.

The characteristic feature of the reaction of the coronary vessels to papaverine in different animals is its great variability. In a dose of 0.5 mg/kg papaverine causes an increase of 10-70% in the rate of the coronary

blood flow. In some animals even greater doses of papaverine do not increase the rate of the coronary blood flow.

With repeated injections of papaverine an increased reaction of the coronary vessels to each successive injection was not observed.

In order to ascertain the role of the cholinergic and adrenergic innervation in the vasodilator effect of papaverine, experiments were performed using atropine and dihydroergotamine. After administration of atropine in a dose of 1 mg/kg the increase in the rate of the coronary blood flow in response to papaverine was approximately the same as before the atropine was given. The reaction of the coronary vessels to papaverine was also unchanged after the injection of 0.5 mg/kg of dihydroergotamine. Thus the effect of papaverine on the rate of the coronary blood flow is evidently independent of the action of this drug on the innervation of the vessels of the heart.

Experiments with Dibazol

Figure 2 represents an experiment in which the effect of dibazol on the rate of the coronary blood flow was most marked. The results of the effect of dibazol on the rate of the coronary blood flow are summarized in Table 1. From this table, and from Fig. 2 it can be seen that the rate of the coronary blood flow is slightly increased by

dibazol for only a very short period of time. In a dose of 20 mg/kg dibazol had less effect than in a dose of 10 mg/kg, on account of the sharp fall in the blood pressure.

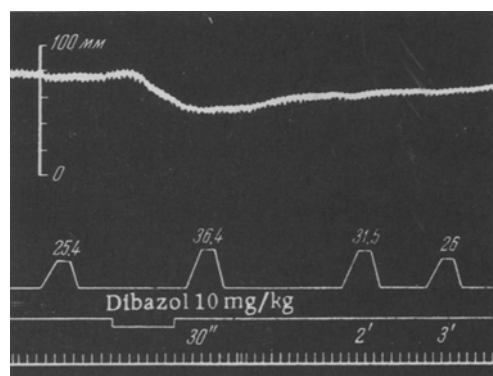


Fig. 2. The effect of dibazol on the rate of blood flow from the coronary sinus. Interpretation as in Fig. 1.

With repeated administration the reaction of the coronary vessels to dibazol was increased. In one experiment dibazol, injected in a dose of 1 mg/kg half an hour after the injection of the same drug in a dose of 15 mg/kg, caused an increase in the rate of the coronary blood flow of 54%, while at the beginning of the experiment a dose of 1 mg/kg was below the threshold level.

Just as in the experiments with papaverine, the preliminary administration of atropine and dihydroergotamine caused no essential changes in the reaction of the coronary vessels to dibazol.

Experiments with Combined Administration of Papaverine and Dibazol

The injection of papaverine immediately after dibazol increases the rate of the coronary blood flow to a greater degree than its use alone. The results of this series of experiments are shown in Table 2. The papaverine was usually injected from 10-15 min after the injection of dibazol. At this time the increase in the rate of coro-

TABLE 2

The Effect of Papaverine on the Rate of the Coronary Circulation Before and After Injection of Dibazol

Expt. no.	Effect of papaverine (0.5 mg/kg) on rate of coronary blood flow in %		Dose of dibazol in mg/kg	Effect of papaverine (0.5 mg/kg) on rate of coronary circulation after injection of dibazol	
	maximum increase in rate of coronary blood flow in %	duration of action in min		maximum increase in rate of coronary blood flow in %	duration of action in min
1	50	20	10	60	60
2	20	5	10	80	10
3	25	10	20	65	10
4	35	10	10	60	20
5	28	10	10	38	20

nary blood flow due to dibazol had completely disappeared. In 2 experiments papaverine was injected 10 min and also one hour after the injection of dibazol. In the latter case the increase in the reaction of the coronary vessels to papaverine was not observed.

With combined administration of papaverine and dibazol an enhanced effect of the drugs on the rate of the coronary blood flow is observed. In one of these experiments in which this effect was most pronounced, papaverine in a dose of 0.5 mg/kg and dibazol in a dose of 2.5 mg/kg when injected simultaneously caused an increase in the rate of the blood flow of 35% which lasted 30 min.

Papaverine alone in the same dose increased the rate of the coronary blood flow by 10% for a period of 10 min, while dibazol increased the rate of the coronary blood flow by 10% for 2 min.

SUMMARY

The effect of papaverine and dibazol on the coronary blood flow was studied in short-term experiments on cats, anesthetized with nembutal in condition of artificial respiration. A method which allowed determination of the volume velocity of blood outflow from the coronary sinus was employed. Papaverine provokes a pronounced increase of the coronary blood flow. Dibazol on the other hand, causes only insignificant and temporary increase. When papaverine was administered after dibazol its effect on the coronary blood vessels was enhanced. Thus, combined administration of papaverine and dibazol reinforces their effect.

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* Original Russian pagination. See C. B. translation.