A PHYSIOLOGICAL ANALYSIS OF THE PROPHYLACTIC ACTION OF DIMEDROL (DIPHENHYDRAMINE HYDROCHLORIDE) IN SHOCK FOLLOWING HETEROGENOUS BLOOD TRANSFUSION

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In a previous report we presented results indicating that the prophylactic action of dimedrol in shock due to transfusion of heterogenous blood is largely due to its property of increasing the excitability of adrenergic systems and of lowering to some extent the excitability of the cholinergic systems of the body.

Bearing in mind that dimedrol causes moderate depression of the N-cholinergic systems of autonomic ganglia [9], we undertook the task of investigating whether the prophylactic effect of dimedrol in heterogenous blood transfusion shock is dependent on the state of the synaptic transmission in the autonomic ganglia.

The blocking action of dimedrol was investigated by means of pachycarpine hydriodide. According to many writers [2-4, 8, 9, 11], this substance has a paralyzing action on N-cholinergic structures, accompanied by interference with the transmission of impulses in the ganglia of the autonomic division of the nervous system. Pachycarpine diminishes the sensitivity of the chromaffin tissue of the adrenals and carotid bodies to chemical stimuli [8]. In addition, its application leads to stimulation of the protective inhibition in the cerebral cortex [3] and to disturbance of the transmission of impulses in the efferent pathways and, in particular, in the ganglia of the sympathetic nervous system, as a result of which the pressor effect is suppressed and the blood vessels are dilated.

EXPERIMENTAL METHOD

Experiments were carried out on dogs under morphine anesthesia. Morphine was injected subcutaneously in a dose of 0.5 ml of a 1% solution per 1 kg body weight 35-45 min before the beginning of the experiment. Experimental heterogenous blood transfusion shock was caused by the intravenous injection of citrated rabbits' blood in a dose of 10 ml/kg body weight. The prophylactic dose of dimedrol (15 mg/kg body weight) was injected intramuscularly 15-20 min before the injection of the citrated rabbits' blood. The principal criteria used were the arterial pressure, respiration, the general conditions of the animal, and the state of the pupillary and corneal reflexes, which were studied before and after the injection of the prophylactic substances, and also after injection of the citrated rabbits' blood at intervals of 15, 30, and 45 min. The arterial pressure was measured in the femoral artery. Respiration was recorded through a glass tube inserted into the animal's nostril and connected to a Marey's capsule. Three series of experiments were conducted, one control and two principal.

EXPERIMENTAL RESULTS

In the control experiments we studied the state of the circulation and respiration in healthy animals receiving intramuscular injections of pachycarpine, in a dose of 0.03 g/kg body weight, followed after 15 min by dimedrol in the accepted dosage. The intramuscular injection of pachycarpine led to a very slight lowering of the arterial pressure, whereas the supplementary injection of dimedrol always led to an increase in the pressure (Table 1).

Because of the considerable increase in the arterial pressure, the tachycardia, the dilatation of the pupils, and the disappearance of the narcotic effect of the morphine, we were led to suppose that dimedrol, in this dosage, excites the sympathetic division of the autonomic nervous system, despite the blocking of the N-cholinergic systems of the sympathetic ganglia due to the action of pachycarpine. Having demonstrated by these experiments the ability of pachycarpine to potentiate the action of dimedrol and to bring about a persistent elevation of the arterial pressure

in the control animals, we turned to the study of the prophylactic action of this combination of drugs in heterogenous blood transfusion shock (Table 2).

As an illustration of the typical hemodynamic changes after the prophylactic injection of the drug combination (pachycarpine + dimedrol) we present the kymogram of an experiment (see figure) on a male dog weighing

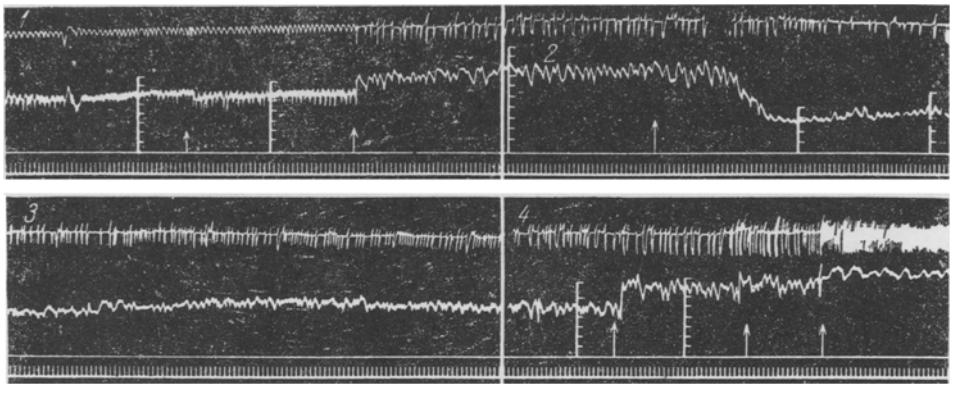
TABLE 1. Changes in the Arterial Pressure in Animals Receiving Dimedrol to Supplement the Action of Pachycarpine

Statistical criterion	Arterial pressure (in mm Hg)				
	initial	at the time of injection of dimedrol	after injection of dimedrol		
			15 min	30 min	45 min
M ± m	108.5 ± 1.64	107.3 ± 4.9	132 ± 9.9	129 ± 10.2	131 ± 10.8

TABLE 2. Changes in the Arterial Pressure in Heterogenous Blood Transfusion Shock after Treatment with Combination of Pachycarpine and Dimedrol

Statistical criterion	Arterial pressure (in mm Hg)						
	initial	15 min after injection of pachycarpine	15 min after injection of dimedrol	time after injection of blood			
				at moment of maximal fall of pressure	15 min	30 min	45 min
M ± m	94.4 ± 6.8	88.4 ± 7.42	127 ± 12.5	20 ± 5.07	104.4 ± 11	120.4 ± 7.5	130.1 ± 12.5

20.1 kg (the arterial pressure was measured in the femoral artery). In order to discover if the order of administration of this combination of drugs affected its propylactic action, in a third series of experiments we injected dimedrol intramuscularly, and followed this after an interval of 15 min with an injection of pachycarpine hydriodide (Table 3).



Changes in the arterial pressure in heterogenous blood transfusion shock caused by treatment with a prophylactic combination of pachycarpine + dimedrol. Significance of the curves: respiration; arterial pressure; zero line; time marker (3 sec). 1) 15 min after intramuscular injection of pachycarpine; 2) 15 min after intramuscular injection of dimedrol; 3) intravenous injection of blood; 4) end of injection of blood.

The injection of rabbits' blood into the dogs was accompanied by a slight fall in the arterial pressure, followed by a rapid recovery (see Table 3). The main fall in pressure took place at the moment of injection of the foreign blood, and the maximal fall varied in individual dogs from 32 to 92 mm. At intervals of 15, 30, and 45 min after injection of the rabbits' blood the arterial pressure in all the dogs was much higher than the initial level.

Administration of these drugs (pachycarpine before dimedrol) was followed by aggravation of the course of the heterogenous blood transfusion shock. This took the form of a more marked fall in arterial pressure, depression of the reflex reactions, and profound changes in the animal's general condition. The maximal fall of the blood pressure in these experiments varied between 6 and 34 mm. The restoration of the arterial pressure during the first 15 min after the heterogenous transfusion took place more slowly than after administration of the drugs in the opposite order, with dimedrol before pachycarpine.

TABLE 3. Changes in the Arterial Pressure during Heterogenous Blood Transfusion Shock after Treatment with a Combination of Dimedrol and Pachycarpine

Statistical criterion	Arterial pressure (in mm Hg)						
	initial	15 min after injection of pachycarpine	15 min after injection of dimedrol	time after injection of blood			
				at moment of maximal fall of pressure	15 min	30 min	45 min
M ± m	103 ± 3.8	129 ± 4.4	113.2 ± 7.7	48 ± 12.9	109 ± 9.08	127 ± 7.01	132.4 ± 4.9

Hence, depending on the order of administration of these drugs, the course of heterogenous blood transfusion shock was modified. When dimedrol exerted its action against the background of the effect of pachycarpine, its prophylactic effect was diminished. If the drugs were given in the opposite order, the prophylactic effect of dimedrol was enhanced by the subsequent administration of pachycarpine. Bearing in mind the pharmacodynamic properties of these drugs, it may be assumed that the mechanism of the prophylactic action of dimedrol depended to a lesser degree on the blocking of the N-cholinergic systems of the autonomic ganglia. This accounted for the fact that pachycarpine—a drug blocking the N-cholinergic systems of autonomic ganglia,—if injected before dimedrol, did not enhance but, on the contrary, diminished the beneficial effect of dimedrol in heterogenous blood transfusion shock.

Incidentally, we may note that the sedative aspect of the action of dimedrol, intensified by administration of pachycarpine, was probably not responsible for the prophylactic effect of dimedrol in heterogenous blood transfusion shock.

The experiments described above confirm our previous suggestion [10] that the prophylactic effect of dimedrol is determined by its property of exciting the peripheral adrenergic and cholinergic systems of the organisms.

SUMMARY

Experiments were staged on 20 dogs under acute conditions. A study was made of the prophylactic effect exerted by dimedrol in heterogeneous blood shock in conditions of its combined administration with pachycarpine. Pachycarpine-dimedrol combination proved to diminish the prophylactic effect of dimedrol. A reverse order of administration of these preparations intensified the prophylactic effect of dimedrol. The analysis of the results obtained and the pharmacodynamic features of the agents used led to a conclusion that the prophylactic effect of dimedrol did not depend on its depressive properties upon the N-cholinergic system or on its sedative action. Thus, a formerly drawn conclusion was confirmed in these investigations, i.e., that the mechanism of the prophylactic effect produced by dimedrol in heterogeneous blood shock was mainly determined by its capacity to enhance the excitability of the peripheral adrenergic systems and to diminish the excitability of body cholinergic systems.

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