THE EFFECT OF CHLORPROMAZINE ON THE COAGULATION OF THE BLOOD AND THE ARTERIAL PRESSURE

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The stimulation of excitation in the cerebral cortex is accompanied by a slowing of the coagulation of the blood, and stimulation of inhibition in the cortex by a corresponding acceleration [8]. Strong excitation of the nervous system increases the heparin activity, and in the normal state of this system the activity of the tissue thrombokinase is increased [4]. Mental excitation of patients due to an impending operation has been shown to depress the thermal coagulability of the serum by F. S. Okolov's method [11].

The stimulating action of sedatives and hypotensive drugs, such as bromide [18], Lagochilus inebrians [1, 2], gendon, reserpine, redergam, magnesium sulfate, Eucommia ulmoides [9], and other preparations, on the coagulation of the blood may be taken as established; meanwhile Panax ginseng, which excites the central nervous system, may cause bleeding [3, 5].

Adrenalin is usually regarded as accelerating the coagulation of the blood, although in large doses it retards this process [6]. Some writers ascribe a similar action to adrenolytic substances, notably chlorpromazine. Admittedly, there is some difference of opinion regarding the effect of chlorpromazine: some writers consider that it has a transient accelerating action [13], others—a retarding action [10, 12], while a third group asserts that it may promote thrombosis and embolism [15-18].

We have investigated the effect of chlorpromazine on the coagulability of the blood in experiments on animals.

EXPERIMENTAL METHOD

Experiments were conducted on 15 dogs, of which 5 were controls. Each animal received an intravenous injection of 1 ml of a 2.5% solution of chlorpromazine, constituting from 3.6 to 1.2 mg/kg body weight for the different animals.

Before the drug was given, initial recordings of the arterial pressure in the femoral artery were made by means of a mercury manometer, and the clotting time of the blood was measured by Fonio's method, the plasma recalcification time by Bergerhof and Rocca's method, the plasma heparin tolerance by Poller's method, the Ac-globulin by Lewi and Weirf's method, and the proconvertin by Owren and Aas's method. When the initial values of these indices had been established, the experimental animals received an intravenous injection of chlorpromazine, and the controls the same volume of physiological saline. Blood was taken after 15, 30, and 60 min for measurement of the clotting time and the level of the arterial pressure was recorded.

EXPERIMENTAL RESULTS

The intravenous injection of chlorpromazine in these doses led to a lowering of the arterial pressure at each time of observation. Statistical analysis of the results showed that the hypotensive action of chlorpromazine in dogs was significant ($P < 0.01$). At the same time, chlorpromazine had a stimulating action on the coagulability of the blood, although in most animals this effect followed a transient slowing of the process. A biphasic action of this sort was observed in six dogs. It should be noted that the phase of slowing (judging by the three animals in which the rate of clotting was investigated more frequently than in the other dogs) began only 15 min after the administration of chlorpromazine.

TABLE 1. Relationship between the Rate of Clotting of the Blood (Fonio's method) and the Action of Chlorpromazine (as percentages of the initial values)

Dog	Dose of preparation (in mg/kg)	Time after injection of drug (in min)		
		15	30	60
Zhuchok	3.6	+85	−39	−56
Tigrenok	2.5	−42	−55	−50
Dozor	2.3	+50	−27	−30
Vertushka	2.1	−2	−65	−66
Mos'ka	2.1	−41	−75	−83
Bobka	2.1	+6	−12	+6
Pamir	1.9	−18	−64	−71
Damka	1.8	+200	+81	+22
Merka	1.5	+66	−73	−80
Barbos	1.2	+22	−53	−61

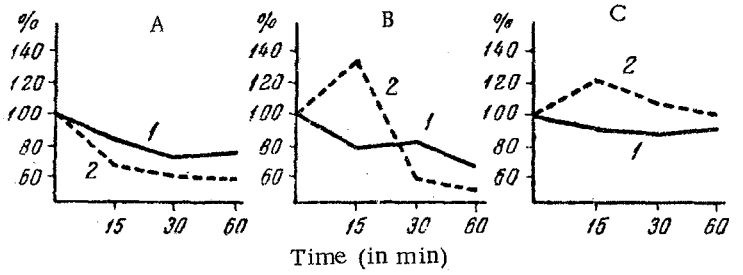
TABLE 2. Effect of Chorpromazine on the Coagulation of the Blood and Arterial Pressure

Tests	Statistical criteria	Chlorpromazine				Physiological saline (control)			
		initial level before injection	time after injection of prep. (min)			initial level before injection	time after injection of prep. (min)		
			15	30	60		15	30	60
Clotting time (Fonio)	*M*	436	602	233	203	460	472	356	344
	m±	75	78	43	40	121	106	107	102
	P	—	<0,2>0,1	=0,05	<0,02	—	>0,5	<0,5	<0,5
	n	10	10	10	10	5	5	5	4
Plasma recalcification time	*M*	33	29	21	18	59	46	56	53
	m±	4	5	3	3	6	13	15	26
	P	—	<0,5	<0,02	<0,01	—	<0,5	>0,5	>0,5
	n	10	10	10	10	5	5	5	4
Plasma heparin tolerance	*M*	53	48	27	21	90	73	68	100
	m±	14	16	5	3	37	50	23	58
	P	—	<0,5	<0,2	<0,05	—	>0,5	>0,5	>0,5
	n	10	10	10	10	5	5	5	4
Ac-globulin	*M*	39	39	34	37	43	43	47	36
	m±	4	5	5	5	5	7	7	5
	P	—	0	<0,5	>0,5	—	0	>0,5	>0,2
	n	10	10	10	10	5	5	5	4
Proconvertin	*M*	41	41	41	41	42	48	46	60
	m±	3	3	4	4	15	15	15	21
	P	—	0	0	0	—	>0,5	>0,5	>0,5
	n	10	10	10	10	5	5	5	4
Mean arterial pressure (mm Hg)	*M*	149	123	114	107	116	109	108	111
	m±	4	5	5	5	13	13	13	13
	P	—	<0,01	<0,01	<0,01	—	<0,7	<0,7	<0,7
	n	10	10	10	10	5	5	5	4

Note. M−arithmetical mean; m± −mean error; P−probability of significance of difference; n−number of experimental animals.

In only one of the six dogs (Damka) was the clotting of the blood delayed 30 and 60 min, as well as 15 min, after injection of chlorpromazine, although 70 min after the injection the rate of coagulation of the blood in this dog, too, was increased by 30%, and by 11% after 80 min, compared with the initial values.

It is clear from Table 1 that after intravenous injection of chlorpromazine the clotting time of the blood was considerably shortened in all the dogs. The action of the drug on the coagulation of the blood, as on the arterial pressure, was not proportional to the size of the dose: in Barbos, 30 and 60 min after the injection of chlorpromazine in a dose of 1.2 mg/kg the rate of clotting of the blood increased by 53 and 61%, respectively, and in the dog Zhuchok, receiving a dose of 3.6 mg/kg, by 39 and 56%, respectively.



Changes in the arterial pressure (1) and the rate of clotting of the blood (2) after administration of chlorpromazine. A) Injection of chlorpromazine in a dose of 2.5 mg/kg (the dog Tigrenok); B) injection of chlorpromazine in a dose of 1.2 mg/kg (the dog Barbos); C) control, injection of physiological saline (the dog Sultan).

Chlorpromazine had a well marked hypotensive action, while at the same time stimulating the process of coagulation of the blood (Table 2). The latter was reflected in the shortened clotting time (Fonio) and recalcification time of oxalated plasma, and in the increased plasma heparin tolerance. Chlorpromazine had no effect on the concentration of Ac-globulin and proconvertin in the blood.

In some cases (see figure, A) the effect of chorpromazine was characterized by a progressive lowering of the arterial pressure, and by an initial slowing, followed by an acceleration of the coagulation of the blood (shown by the broken line), while in other cases (see figure, B) the arterial pressure was lowered and the clotting time of the blood was shortened. In the control animals (see figure, C) the level of the arterial pressure and the rate of coagulation of the blood were only very slightly changed.

This investigation gives no clue to the mechanism of the effect of chlorpromazine on the coagulation of the blood. However, the stimulating action of this preparation on this process indicates that the acceleration of clotting may result not only from activation of the sympathetico-adrenal system or the action of adrenalin, but also from the effect of substances possessing an adrenolytic action.

SUMMARY

There are many scientific papers disapproving the well-known statement of Connon that emotions stimulate blood coagulation. Not excitation, but intensification of the inhibitory process in the cerebral cortex is accompanied by stimulation of the blood coagulation process. It is also known from literature (I. A. Akopov) that general hemostatic and sedative properties in medicinal substances are regularly conjoint. A combination of hypotensive properties with the acceleration of blood coagulation was also noted (gendon, reserpine, redergam etc. – Kochetkova).

Literature data on the effect of chlorpromazine on the process of blood coagulation are controversal. Up to the present time large doses of this preparation were used experimentally. The authors studied the effect of chlorpromazine in a dose of 1-2.5 mg/kg on 15 dogs and came to the following conclusions: 1) Intravenous administration of chlorpromazine to dogs accelerates the blood oxalate coagulation time, increases the plasma tolerance to heparin. 2) Chlorpromazine produces no effect on the blood Ac-globulin and proconvertin content. 3) The action of chlorpromazine is biphasic: during the first brief phase it retards, and during the second more prolonged one – accelerates the process of blood coagulation.

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