EFFECT OF PARMIDINE (PYRIDINOLCARBAMATE) ON PLATELET AGGREGATION, BLOOD COAGULATION, AND FIBRINOLYSIS

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The effect of Parmidine (pyridinolcarbamate) on platelet aggregation, blood coagulation, and fibrinolysis was studied in rabbits. After direct addition of Parmidine to platelet-enriched plasma aggregation of the platelets produced by serotonin (5-HT) and adrenalin was reduced. After oral administration of Parmidine to animals, aggregation induced by ADP, 5-HT, and adrenalin was inhibited, blood coagulation was reduced, and fibrinolysis was accelerated.
KEY WORDS: *Parmidine (Anginin, pyridinolcarbamate); platelets; fibrinolysis.*

Pyridinolcarbamate, or 2,6-pyridinemethano-bis-N-methylcarbamate, has been suggested by Japanese workers [16] under the name of "Anginin" for the treatment of diseases associated with atherosclerotic vascular lesions. Anginin has an inhibitory effect on platelet aggregation [18]. This property of pyridinolcarbamate is evidently of great importance in the mechanism of its therapeutic action, for changes in the blood clotting system and increased platelet aggregation are ascribed great importance in the pathogenesis of the early stages of atherosclerosis [19] and its thrombotic complications in the late stages of the disease [2].

TABLE 1. Effect of Parmidine and Anginin on Platelet Aggregation *in Vitro* (M±m)

Preparation	Dose (in mg/kg)	Platelet aggregation (in % of lowering of optical density)			
		ADP		serotonin and adrenalin	
		−	+	−	+
Parmidine	0,05	49,0±4,1	33,0±6,4*	42,0±2,7	21,0±5,9*
	0,15	49,0±4,1	31,0±7,1*	42,0±2,7	26,0±6,4*
	0,3	49,0±4,1	41,0±3,0	42,0±2,7	35,0±5,4*
Anginin	0,05	49,0±4,1	26,0±2,3*	42,0±2,7	27,0±4,1*
	0,15	49,0±4,1	30,0±6,8*	42,0±2,7	26,0±6,4*
	0,3	49,0±4,1	42,0±5,1	42,0±2,7	25,0±6,1*

Legend. Here and in Tables 2 and 3: − and + denote absence and presence of the substances respectively.

*Here and in Tables 2 and 3 values of $P < 0.05$ given compared with the control in the absence of the substances.

Pyridinolcarbamate has been synthesized at the S. Ordzhonikidze All-Union pharmaceutical Research Institute and, after clinical trials, has been accepted for use in medical practice under the name of "Parmidine." The next step was therefore to study the effect of Parmidine and Anginin on platelet aggregation and also on blood coagulation and fibrinolysis.

EXPERIMENTAL METHOD

Experiments were carried out on rabbits of both sexes weighing 2-4 kg. Platelet aggregation was determined by Born's method [3] with graphic recording by O'Brien's method [12]. The method consists of determining changes in the optical density of platelet-enriched plasma (during platelet aggregation), induced by various substances: ADP, serotonin (5-HT) and adrenalin. The state of blood coagulation was

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TABLE 2. Effect of Parmidine and Anginin on Platelet Aggregation *in vivo* (M±M)

Preparation	Dose (in mg/kg)	Platelet aggregation (in % of lowering of optical density)							
		ADP				serotonin and adrenalin			
		–	+			–	+		
			1 h	3 h	5 h		1 h	3 h	5 h
Parmidine	5	43,5±4,8	28,6±6,4*	34,0±7,1	—	36,0±2,5	24,0±2,2*	29,0±6,2	—
	15	59,0±3,2	36±5,85*	36,0±7,1*	47,0±8,3	41,0±3,4	16,5±3,5*	21,0±4,6*	36,0±7,4
	30	50,0±1,7	37,3±3,4*	34,5±3,8*	43,0±6,7	40,0±4,2	19,7±5,9*	21,0±7,0	29,0±9,6
Anginin	5	44,0±2,6	40,0±6,4	38±2,8	—	31,0±4,3	27,0±7,1	26,0±7,7	—
	15	44,0±4,2	40,0±4,7	31,0±6,3*	46,0±7,8	36,0±4,08	28,0±2,3*	22,3±4,3*	37,0±7,6
	30	42,5±3,4	33,0±5,6*	34,6±6,0*	37,0±4,7	35,0±1,8	22,0±3,3*	19,7±5,5*	31,0±7,8

estimated by determination of the activity of the prothrombin complex by Quick's method, and the blood recalcification time, and by recording the thromboelastogram on the "Hellige" apparatus. Fibrinolysis was determined by Donner's method [7].

The test substances were given to the animals by mouth in doses of 5, 15, and 30 mg/kg; in concentrations of 0.05, 0.15, and 0.30 mg/ml they were added directly to the platelet-enriched plasma in the cell of the apparatus. Observations on platelet aggregation were made with the FEK-M photoelectric colorimeter and the KSP-4 automatic-writing potentiometer.

EXPERIMENTAL RESULTS AND DISCUSSION

Both after direct addition of Parmidine and Anginin to platelet-enriched plasma and after their oral administration to the animals, aggregation of the platelets and blood coagulation diminished. The two substances had practically identical effects. In particular, Parmidine and Anginin, in concentrations of 0.05 and 0.15 mg/ml, when added to platelet-enriched plasma, reduced platelet aggregation induced by 5-HT and adrenalin but had no effect on aggregation induced by ADP (Table 1). After oral administration of Parmidine to the animals in doses of 5, 15, and 30 mg/kg, platelet aggregation induced by ADP, 5-HT, and adrenalin also was reduced. Anginin, given in doses of 15 and 30 mg/kg, had the same effect. Both preparations acted 1 and 3 h after administration (Table 2).

Paridine and Anginin in experiments *in vivo* led to a moderate decrease of blood coagulation which was statistically significant, although much less than that of the known anticoagulants. The depression of blood coagulation was manifested as a decrease in the activity of factors of the prothrombin complex in Quick's test and lengthening of the blood recalcification time (Table 3). The reaction time, reflecting the period of formation of active thrombin and thromboplastin, and the clot-formation time, characterizing the initial period of thrombus formation, were lengthened on the thromboelastograms, and the amplitude of the thromboelastograms, which taken as a whole depends on the functional state of the platelets and the fibrinogen concentration, was somewhat reduced. Fibrinolysis of the clots was accelerated 1 h after administration of the drugs and reached a maximum after 3 h; after 5 h it returned to its initial level.

TABLE 3. Effect of Parmidine and Anginin *in vivo* on Thromboplastin Time and Recalcification Time of the Blood (M±m)

Preparation	Dose (in mg/kg)	Thromboplastin time (in sec)				Blood recalcification time (in sec)			
		–	+			–	+		
			1 h	3 h	5 h		1 h	3 h	5 h
Parmidine	5	7,6±0,4	7,8±0,7	7,6±0,5	—	49,0±4,6	57,0±6,7	99,0±7,7*	59,0±6,1
	15	6,25±0,7	6,9±0,5	7,7±0,6	6,5±0,7	54,0±5,8	66±6,4	87,0±7,7*	52,0±3,4
	30	7,3±0,2	7,8±0,2	10,9±0,4*	8,1±0,9	57,0±2,0	79,0±4,7*	65,0±7,4	60,0±4,2
Anginin	5	6,3±0,4	8,7±0,6*	9,7±0,3*	7,1±0,9	41,0±5,8	57,0±4,1*	119,0±8,6*	60,0±7,7
	15	7,8±0,5	8,4±0,5	8,7±0,6	7,4±0,6	50,6±7,7	64,0±8,2	73,0±6,5*	54,0±6,4
	30	6,6±0,2	8,6±0,2*	8,6±0,3*	7,6±0,4	48,0±6,0	72,0±4,2*	65,0±6,4*	59,0±6,7

Parmidine, like the Japanese preparation Anginin [13, 14, 16, 18], thus induces a statistically significant decrease in platelet aggregation. It was interesting to note that the antiaggregation action of Parmidine was more marked when given to the animals by mouth than when added directly to platelet-enriched plasma. This phenomenon is probably due to the indirect action of Parmidine on platelet aggregation in the intact organism, more especially because its action on aggregation and fibrinolysis takes place at the same time. Some fibrinolytic and fibrinogenolytic substances are known to reduce platelet aggregation as a result of the accumulation of degradation products of fibrinogen in the plasma [15]. At the same time, another mechanism of the observed decrease in platelet aggregation under the influence of Parmidine can be suggested. During contact between blood and glass, the rapid formation of kinins [6, 8], which themselves induce platelet aggregation [15], is observed. Platelet aggregation in the present experiments is evidently a composite phenomenon, induced by the addition of adrenalin and by kinins formed during contact with the glass cell wall, and Parmidine is an antagonist of the kinins [17].

Energy processes also play an important role in the mechanism of the antiaggregation and fibrinolytic action of Parmidine. Parmidine is known to activate cell glycolysis [16], and this in turn can lead to changes in the ATP:ADP ratio in the platelets. A shift of this ratio toward an increase in the ADP concentration largely determines the tendency of platelets to form conglomerates [4].

The decrease in platelet aggregation and increase in fibrinolysis, as well as some increase in the thromboplastin time, are favorable factors in the treatment of atherosclerosis, for this disease is accompanied by increased ability of the platelets to aggregate, an increase in the activity of the clotting system, and depression of fibrinolysis [2, 11].

Considering the marked effect of Parmidine on the system of hemostasis, during treatment with this substance a regular check must be kept on the indices of blood coagulation.

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