THE EFFECT OF HYDROGENATED ERGOT ALKALOIDS ON THE COAGULATION OF THE BLOOD

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During recent years many papers have been published reporting the accelerating action of sedative and hypotensive drugs on the coagulation of the blood. It has been found that substances with a sedative and hypotensive action such as Lagochilus inebrians [2], sodium bromide [10, 18], reserpine, hydergine, magnesium sulfate, Eucommia ulmoides, salsolin [7, 8], Rausedil [5], chlorpromazine [4, 11], and nicotinic acid [1, 12, 13] stimulate this process.

The study of the action of the hydrogenated alkaloids of ergot on the process of blood coagulation is of great interest. The adrenolytic and hypotensive properties of the ergot alkaloids are known to be considerably enhanced by reduction to the hydrogenated derivatives [14]. There are few references in the literature to the action of ergot alkaloids on blood coagulation, and such information as can be found is conflicting. According to A. A. Markosyan [9], the intravenous injection of ergotin has no significant effect on the clotting time of the blood. Hladovec and Votava [15] showed that ergotamine and ergometrin shorten the clotting time of the blood in experiments in vitro, and Rossano and Legeza [17] used hydergine successfully in the treatment of severe hemorrhage from the gastro-intestinal tract. Meanwhile Königs [16] used pantesin-hydergine in the treatment of patients with thrombosis and embolism.

The object of the present investigation was to study the influence of dihydroergotoxin and dihydroergotamine on the process of coagulation of the blood.

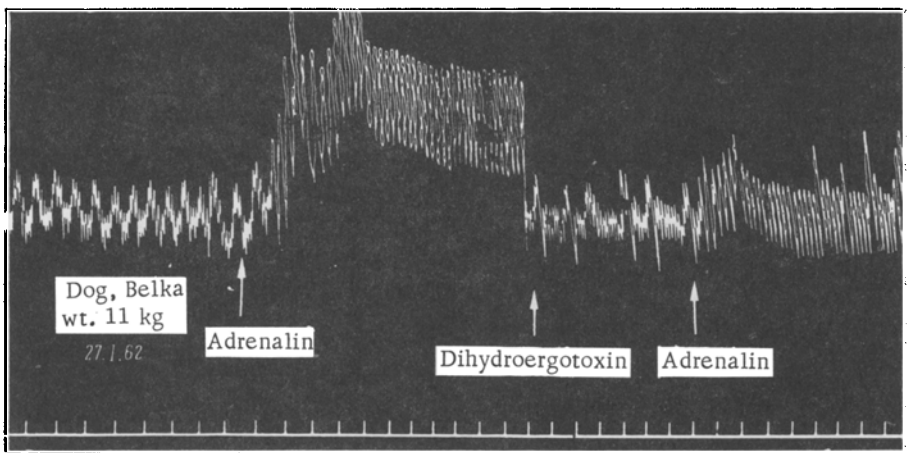

Fig. 1. Changes in arterial pressure of a dog after intravenous injection of adrenalin in a dose of 0.03 mg/kg before and after injection of dihydroergotoxin in a dose of 0.08 mg/kg. Significance of curves (from top to bottom): arterial pressure, time marker (5 sec).

EXPERIMENTAL METHOD

Acute and chronic experiments were conducted on 48 intact dogs. Dihydroergotoxin was injected intravenously in the acute experiments in doses of 0.01, 0.02, 0.04, and 0.08 mg/kg, and dihydroergotamine in the same conditions in a dose of 0.02 mg/kg. In the chronic experiments dihydroergotoxin was injected subcutaneously in a dose of 0.02 mg/kg daily for 7 days. Control animals received an equal volume of physiological saline.

In order to study the state of the coagulation process, before and at intervals of 30, 60, and 120 min after injection of the preparations the clotting time of the blood was determined by Lee and White's method, the plasma heparin tolerance by Poller's method, the recalcification time of oxalated plasma by the method of Bergerhof and Roca, the prothrombin time by Tugolukov's method, the thromboplastic activity by Kudryashov and Ulitina's method, the fibrinolytic activity by Bidwell's method, and the clot retraction was measured. Besides the blood investigations, recordings were made of the arterial pressure and respiration of the animals. The numerical results of the investigations were analyzed by statistical methods.

EXPERIMENTAL RESULTS

Analysis of the kymograms of the arterial pressure showed that dihydroergotoxin and dihydroergotamine, in the doses which were used, had no hypotensive action. The adrenolytic properties of dihydroergotoxin began to appear when it was given in a dose of 0.02 mg/kg. However, the vascular reaction to intravenous injection of adrenalin was totally abolished only after administration of a dose of 0.08 mg/kg (Fig. 1).

Slowing of the pulse was observed in all the experiments. In some cases a reflex holding of the breath developed at the moment of injection of the dihydroergotoxin. In nearly all the dogs an increase in the tone of the parasympathetic division of the autonomic nervous system was observed after injection of dihydroergotoxin in doses of 0.02-0.08 mg/kg, manifested by an increased salivation and sometimes by vomiting and defecation.

The experimental results showed that intravenous injection of dihydroergotoxin in a dose of 0.01 mg/kg causes a slight acceleration of blood coagulation, demonstrated clearly by a shortening of the recalcification time ($P < 0.05$). The acceleration of the blood coagulation was demonstrated particularly clearly in both acute and chronic experiments when the dose of dihydroergotoxin was 0.02 mg/kg ($P < 0.01$).

The most marked stimulation of the coagulatory system of the blood was observed 60 min after injection of the preparations, when the clotting time was shortened (from 255 to 120 sec), the recalcification time was reduced (from 75 to 44 sec), the plasma heparin tolerance was increased (from 300 to 90 sec), the thromboplastic activity was intensified (from 100 to 146%), and yet an increase in the fibrinolytic activity of the blood was recorded (from 19 to 45%), pointing to the compensatory activation of the anticoagulatory system. The concentration of prothrombin and fibrinogen showed no significant change.

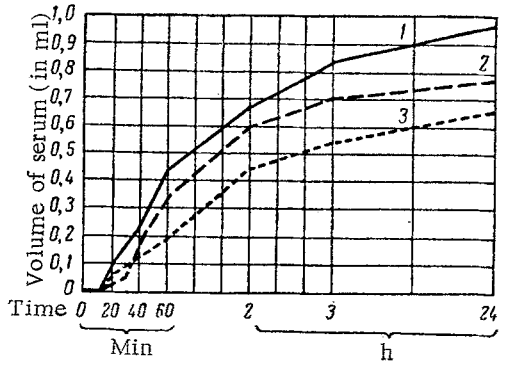

Fig. 2. Rate of clot retraction in normal conditions (1) and after injection of dihydroergotoxin of 0.02 mg/kg (2) and 0.08 mg/kg (3).

An increase in the doses of dihydroergotoxin to 0.04 and 0.08 mg/kg not only did not enhance the accelerating action of the drug on blood coagulation but, on the contrary, weakened it. Administration of dihydroergotamine in a dose of 0.02 mg/kg in the same experimental conditions showed that this compound possesses similar properties to dihydroergotoxin, but that its action is weaker. Control experiments in which physiological saline was injected revealed no changes in the state of the coagulatory system of the blood.

To determine the reason for the absence of the accelerating effect of large doses of dihydroergotoxin on the coagulability of the blood, experiments were carried out on 6 dogs in which dihydroergotoxin was injected in a dose of 0.08 mg/kg after the preliminary intravenous injection of atropine into the animal in a dose of 0.1 mg/kg; several authors [6] have shown that atropine has a blocking action on the anticoagulatory system of the blood. Injection

of dihydroergotoxin after preliminary atropinization of the animal had no accelerating effect on the blood coagulation process. In this series of experiments no increase was observed in the fibrinolytic activity of the blood. Hence, the absence of acceleration of blood coagulation when dihydroergotoxin was given against the background of depression of the anticoagulatory system may evidently be explained by the adrenolytic action of this dose of dihydroergotoxin.

The action of hydrogenated ergot alkaloids on clot retraction was measured by Akopov's universal hemoretractometer [3]. For this purpose venous blood was taken in a volume of 2 ml before and 30, 60, and 120 min after injection of dihydroergotoxin. Observations were made on the retraction for 24 h, readings being taken every 10 min for the first hour, and thereafter at 2, 3, and 24 h. The most marked changes in the course of clot retraction were observed 60 min after injection of dihydroergotoxin.

This drug was found to have an inhibitory action on the retractile properties of the blood clot. The retraction index fell by 22.5% below the normal level with a dose of 0.02 mg/kg of dihydroergotoxin, and by 32.7% with a dose of 0.09 mg/kg.

A distinct difference was observed between the actions of small and large doses: with a dose of 0.02 mg/kg a significant slowing of retraction was recorded during the first 30 min after formation of the clot, while with a dose of 0.08 mg/kg slowing began 30 min after clot formation and was still considerable at the end of the observation (Fig. 2). No regular relationship was noted between the speed of retraction of the blood clot and the rate of blood coagulation. After injection of dihydroergotoxin in a dose accelerating blood coagulation (0.02 mg/kg), and in a dose producing no change in this process (0.08 mg/kg), slowing of clot retraction was observed.

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