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THROMBOLYTIC ACTIVITY OF TERRILYTIN AND ITS EFFECT ON THE BLOOD CLOTTING SYSTEM

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In experiments *in vitro* after preliminary incubation of fibrinogen with terrilytin clot formation was retarded and subsequent lysis accelerated. Terrilytin *in vitro* lengthened the recalcification time, reduced thromboplastic activity and fibrinase activity and, at the same time, increased the fibrinolytic activity of blood plasma. In experiments on dogs roentgenovasography revealed considerable thrombolytic activity of terrilytin when injected intravenously into animals with experimental thrombosis of the femoral veins.

KEY WORDS: *Thrombosis; terrilytin; coagulation; thrombolytic activity.*

Reports have been published [2-5] of the high lytic activity of terrilytin in animals with experimental thrombosis.

During a continuation of these investigations the effect of terrilytin on venous thrombi and on the clotting system of the blood was studied.

EXPERIMENTAL METHOD

In the experiments of series I the effect of terrilytin was investigated on fibrin clots obtained from whole blood, plasma, and fibrinogen by the addition of equal volumes (0.1 ml) of a solution of thrombin with activity 12" (in plasma) to it. The solid clots formed under

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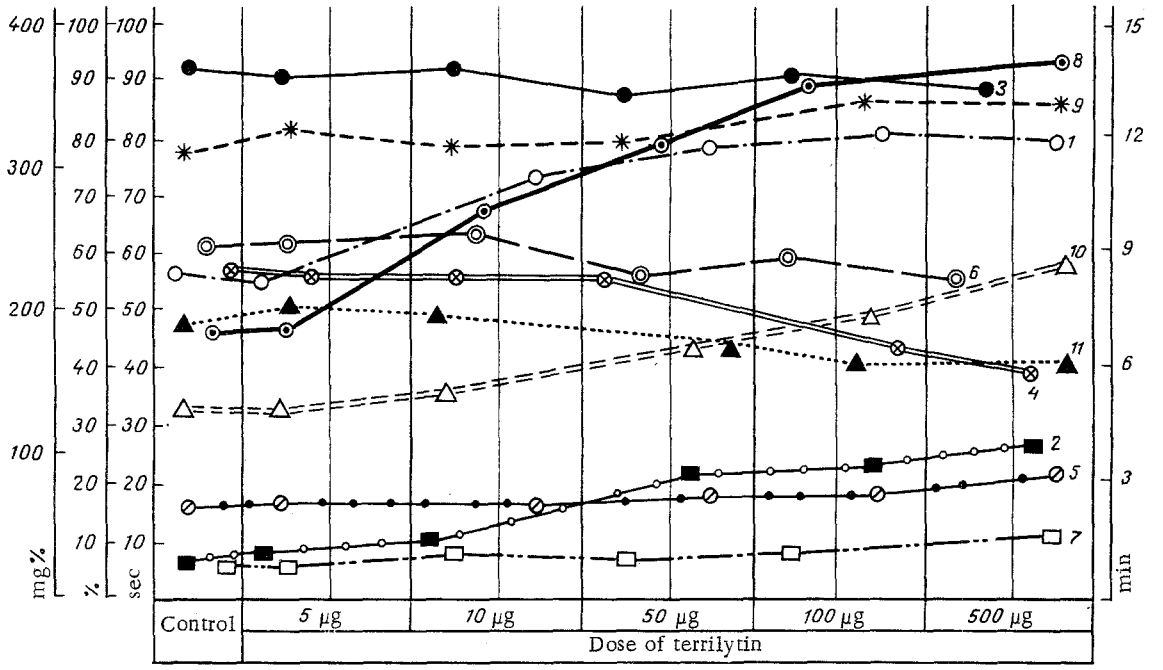

Fig. 1. Effect of terrilvtin on indices of blood clotting: 1) thromboplastin activity (in sec); 2) recalcification time (in sec); 3) prothrombin index (in %); 4) activity of stable factors of prothrombin complex (in %); 5) thrombin time (in sec); 6) heparin time (in sec); 7) free heparin (in sec); 8) plasma heparin tolerance (in min); 9) fibrinogen (in mg %); 10) fibrinolytic activity (in %); 11) fibrinase (in %).

these conditions were immersed in solutions of terrilytin (10 ml) of different concentrations (5, 10, 50, 100, and 500 μg) and incubated at 37°C until lysis was complete. Parallel observations were made on the state of fibrin clots immersed in an equal volume of native plasma (C_1), in plasma incubated with terrilytin (C_2), in plasma with 0.85% NaCl solution (C_3), and also in 0.85% NaCl solution alone (C_4).

In the experiments of series II the effect of terrilytin on the clotting power of blood plasma was studied *in vitro*. For this purpose, plasma obtained in the usual way from five dogs was poured, 9 ml at a time, into 10 test tubes. To half of the tubes 1 ml of terrilytin solution in increasing concentrations (from 5 to 500 μg) was added, whereas the same volume of 0.85% NaCl solution was added to each of the 5 control tubes. After incubation for 30 min at 37°C the indices of blood clotting were determined in all the samples by the usual methods. In the experiments of series III the action of terrilytin was studied on experimental thrombosis of the femoral veins present for 24 h in dogs. Thrombosis was produced by the method described previously [1]. Three experiments were carried out with intra-arterial and 14 with intravenous infusion of terrilytin. The maximal tolerated dose of the substance was 10 mg/kg body weight. The state of the thrombosed area was monitored before and after injection of the terrilytin by contract roentgenovasography, using a 76% solution of verografin (Triosil) (up to 20 ml) and a portable "HIRAX" apparatus with focal length 25 cm, current 10 mA, and exposure 0.8 sec.

EXPERIMENTAL RESULTS

With doses of terrilytin of 50-100 μg lysis of the fibrin clots took place on the average of 8.9±2.0 h, whereas after a dose of 500 μg complete lysis occurred in the course of 2.6±0.4 h. The duration of lysis of clots prepared from fibrinogen in terrilytin solution was reduced (500 μg) to 2.1±0.3 h. Preliminary incubation of fibrinogen with terrilytin (5-10 μg in 0.05 ml) retarded the process of clot formation to some extent and accelerated the subsequent lysis (on the average to 1.4±0.3 h with a dose of 500 μg).

In the control samples (C_1, C_3, and C_4), no sign of lysis of the clots were observed during the 24 h. On incubation of the clots in a mixture of plasma and terrilytin (C_2) doses of this substance of 5-50 μg were ineffective, with a dose of 100 μg lysis of the clot took place in 12.3±1.1 h, with a dose of 500 μg in 3.7±0.9 h.

Within its effective dose range terrilytin clearly lengthened the recalcification time, lowered the thromboplastic activity and fibrinase activity, and also increased the fibrinolytic activity of the blood plasma. At the same time, some decrease in plasma heparin tolerance and an increase in the thrombin time were observed, especially after terrilytin in a dose of 500 μg. Doses of the substance under 100 μg were less active (Fig. 1).

After intra-arterial injection of terrilytin into the animals with experimental thrombosis of the femoral veins, no toxic reactions were observed, and in two of the three dogs complete lysis of the thrombus was observed in one limb. In one dog, roentgenovasography showed only an improvement in the collateral circulation. Intravenous infusion was effective in six of 14 experiments. In five of them complete lysis of the thrombi in both limbs took place.

Roentgenovasographic and radiological investigations showed that by the fifth hour after its administration terrilytin was uniformly distributed in the substance of the thrombus, loosening its structure and inducing its lysis from within. The optimal effect of the preparation occurred after infusion had continued for 4-5 h. The results of isotope studies showed that in this case the maximal terrilytin concentration persisted for a long time in the blood stream.

Terrilytin can thus be regarded as an active thrombolytic agent.

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