The thrombolytic action of terrilytin, a proteinase from Aspergillus terricola, was studied in rabbits with experimental pulmonary thrombosis of 24 hours duration. The preparation was dissolved in polyvinylpyrrolidone and injected into the blood stream in doses of 175 and 220 proteolytic units (PU)/kg body weight by two methods: locally (into the region of the thrombosed vessel), and systemically. Irrespective of the method of administration and dose of the preparation it was found to have high thrombolytic activity, which was more marked, however, after local infusion of terrilytin in a dose of 220 PU/kg. No side effects of the preparation were observed.

KEY WORDS: terrilytin; thrombosis; lung; pulmonary vessels.

The possibility of using terrilytin for the treatment of thromboembolic diseases of the pulmonary circulation was mentioned previously [1, 2]. The idea was based on the results of experiments carried out to study the accumulation and distribution of radioactive terrilytin-125I in experimental animals [1]. In particular, it was shown that 2 h after administration of the preparation maximal levels were found in the heart muscle and lungs; in conjunction with the active uptake of terrilytin into the substance of the thrombus, this suggested that the preparation might well be used with advantage in the treatment of coronary and pulmonary thrombosis.

The first results of an investigation of the effect of terrilytin on the course of experimental pulmonary thrombosis of immune genesis are described below.

EXPERIMENTAL METHOD

Experiments were carried out on 70 Chinchilla rabbits, 10 of which formed the control group.

To produce immunogenic pulmonary thrombosis, the rabbits were treated for several days with microdoses of thrombin together with atropine [3], and when the fibrinolytic activity of the blood was reduced on average by 25-30% (as verified by thromboelastography and in vitro methods [12]), anti-lung immunoglobulins were injected intravenously into the animals. Diffuse aggregation of blood platelets was observed 2-3 h after the injection in the lumen of the pulmonary capillaries and this was followed by the development of thrombosis in the small, medium-sized, and large branches of the pulmonary arteries.

To monitor the development of thrombosis the pulmonary hemodynamics and contractile power of the right ventricle were investigated by recording the intraventricular pressure and by the use of rheo- and polycardiographic methods [5].

Commercial terrilytin was injected into the experimental rabbits on the 2nd day after the development of thrombosis in doses of 175 and 220 proteolytic units (PU) kg/body weight, dissolved in polyvinylpyrrolidone, as a single dose of 5 ml systemically (into the marginal vein of the ear), or locally (into the right ventricle) through a polyethylene catheter. The catheter was introduced under superficial hexobarbital anesthesia (1.5-2.0 ml of 1% hexobarbital solution, intravenously) through the right jugular vein. Control animals received the same volume of polyvinylpyrrolidone. The rabbits were killed 24 h after the injection of terrilytin. The pulmonary vessels were investigated macro- and microscopically. The degree of thrombolysis was calculated as the thrombotic index, in percent [10].

Fig. 1. Thrombolytic activity of terrilytin when administered by different methods. Abscissa, dose of terrilytin (in PU/kg); ordinate, % of thrombosis. A) Control; B and C) systemic infusion; D and E) local infusion. Control: 175 PU/kg. Zone of 100% lysis is shaded.

EXPERIMENTAL RESULTS AND DISCUSSION

All ten rabbits of the control group developed pulmonary thrombosis: in four rabbits the thrombi blocked up to 75% of the pulmonary vascular system with extensive lobar infarcts of the lungs, and in two animals total thrombosis of both pulmonary arteries was observed (Fig. 1). The development of thrombosis was expressed clinically as a sharp decrease in motor activity and an increase in the respiration rate.

Spontaneous lysis of the thrombi was not found in any of the rabbits of the control group.

After injection of terrilytin into the systemic blood flow thrombotic masses were absent in the pulmonary vessels of 10 of the 30 rabbits, four of which had received the preparation in a dose of 175 PU/kg and six in a dose of 220 PU/kg.

Histological examination showed that, despite complete patency of the main trunks in the group of animals receiving terrilytin in a dose of 175 PU/kg, thrombotic masses were still present in the small pulmonary vessels (under 800 μ in diameter); in three cases a hemorrhagic microinfarct of the lungs was found. In four of the 20 rabbits with a negative result of treatment the thrombosis was localized to within 50% of the area of one branch of the pulmonary arteries, in three animals the area of occlusion was 30–35%, in four rabbits 10%, and in nine animals 20–25%. Together with thrombosis, in 12 rabbits multiple foci of necrosis of lung tissue were observed (Fig. 1).

Whatever its dose, the preparation was on the whole well tolerated. Only in five rabbits, receiving terrilytin in a dose of 220 PU/kg, were brief excitation (3–5 min) and isolated twitches of the lower limbs observed.

After local infusion of the preparation (30 rabbits) a positive lytic effect was found in 24 animals; most of them (14 animals) received terrilytin in a dose of 220 PU/kg. In 12 rabbits the large branches of the pulmonary arteries were free from thrombotic masses, but in two animals small fragments of thrombi were present in the lumen of the pulmonary arteries although without affecting the blood flow through them.

Lysis of the thrombi took place in nine of the 15 animals treated with terrilytin in a dose of 175 PU/kg. The pulmonary vessels of one rabbit were occluded by 25% and those of five rabbits by 5–10% (Fig. 1). No toxic manifestations were observed. Meanwhile, after administration of terrilytin in a dose of 220 PU/kg, very small perivascular hemorrhages were found histologically, but were less frequent in the experiments with the smaller dose of the preparation.