EFFECT OF PARMIDINE (PYRIDINOL CARBAMATE) ON MICROVASCULAR PERMEABILITY IN THE LUNGS, SKIN, AND MESENTERY

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The effect of parmidine (pyridinol carbamate) on microvascular permeability in various organs was studied by the use of different models of increased vascular permeability in experiments of mice and rats. Parmidine was shown to have a normalizing action of increased vascular permeability due to the antibradykinin properties of the compound. The results of this investigation correlate with clinical data obtained during the treatment with parmidine of patients with various diseases accompanied by microcirculatory disturbances.

KEY WORDS: parmidine, antibradykinin agent; vascular permeability.

The important role of the kinin system of the body in the regulation of blood flow and microvascular permeability has been demonstrated in an extensive experimental and clinical material [3, 6, 11, 13, 15]. It is accordingly interesting to study the effect of parmidine (pyridinol carbamate), a kinin antagonist, on microvascular permeability in different vascular regions: the lungs, mesentery, and skin.

EXPERIMENTAL METHOD

The effect of parmidine on microvascular permeability in the lungs was studied in male mice weighing 20-22 g with experimentally induced adrenalin edema of the lungs [12]. Adrenalin was injected into the lateral caudal vein in a dose of 50 μg/kg body weight, the animals were killed 5 min later, the lungs were removed and weighed, and their weight relative to the body weight (lung index) was calculated. Parmidine, in doses of 10, 25, and 50 μg/kg, was administered by gastric tube as a 1% aqueous solution 60 min before injection of adrenalin. Each dose of parmidine was given to 10-12 mice.

The effect of parmidine on microvascular permeability in the skin was studied in male rats weighing 140-160 g. Under superficial ether anesthesia, 0.6 ml of a 2% solution of the dye Evans' blue was injected intravenously (into the jugular vein); 1 min later 0.1 ml of a 0.01% solution (10 μg) of bradykinin or histamine was injected into an area of depilated skin of the abdominal wall symmetrically to the right and left of the midline. Each substance was injected at four points of the skin surface. The rats were killed 30 min later, the abdominal skin was excised, and the diameter of the stained papules was measured by means of calipers [10]. Parmidine, in doses of 10, 25, and 50 μg/kg, was given by the method described above 60 min before the bradykinin and histamine. The action of each dose of parmidine was tested on six animals. Rats of the control group (eight animals) received 1 ml of isotonic sodium chloride solution.

The effect of parmidine on microvascular permeability in the mesentery was studied on 20 male rats weighing 180-200 g, in which aseptic peritonitis was induced by intraperitoneal injection of 1 ml of 0.2% silver nitrate. Disturbances of mesenteric microvascular permeability were determined using the ink method, by injecting 0.25 ml purified ink per 100 g body weight intravenously, 3 h after injection of the silver nitrate.

To assess the disturbances of mesenteric microvascular permeability quantitatively two methods were used: 1) the method suggested by the writers previously [2], and 2) analysis by means of a television analyzing systems (TAS, from Leitz, West Germany) and subsequent calculation with the Hewlett-Packard 9810A computer [7]. To assess the extent of involvement of the blood vessels, a coefficient K was used: the ratio of the

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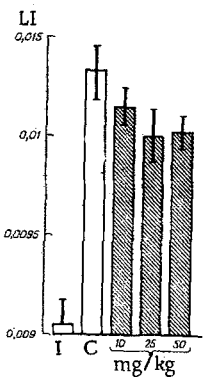

Fig. 1

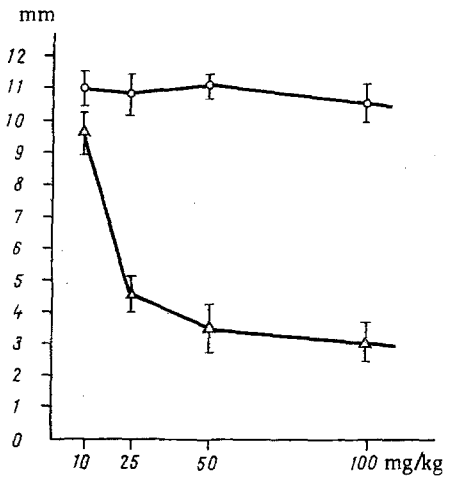

Fig. 2

Fig. 1. Effect of parmidine on lung index (LI) in mice with pulmonary edema caused by intravenous injection of adrenalin. Columns represent values of LI in intake animals (I), control (C), and after oral administration of parmidine in doses of 10, 25, and 50 mg/kg.

Fig. 2. Effect of parmidine on severity of disturbance of permeability of skin capillaries caused by histamine and bradykinin in rats. Abscissa, dose of parmidine (in mg/kg); ordinate, diameter of stained papules (in mm). Each point on graph corresponds to arithmetic mean of measurements of four papules in six animals.

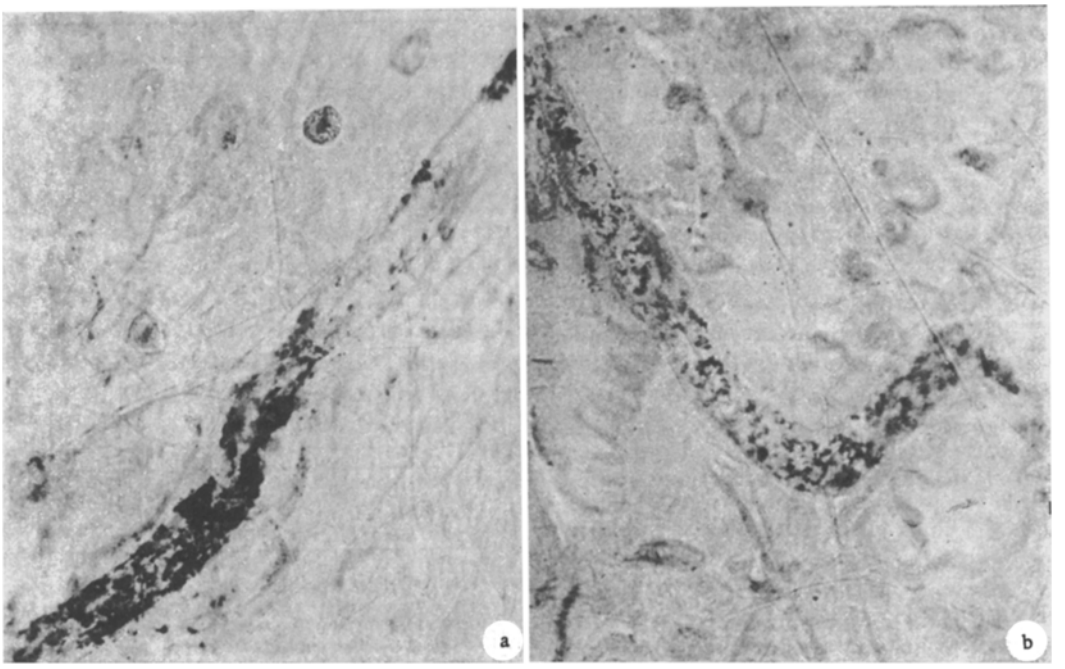

Fig. 3. Normalizing action of parmidine on mesenteric microvessels in peritonitis induced by silver nitrate in rats. Deposition of colloidal carbon particles in a venule in control (a) and after preliminary administration of parmidine in a dose of 50 mg/kg (b). Magnification 100×.

TABLE 1. Effect of Parmidine on State of Mesenteric Microvascular Permeability in Aseptic Peritonitis

Series of experiments	Number of mesenteric windows with labeled vessels (1% of total number examined)			Number of rats with different degrees of labeling (% of number of animals in experiment)				
	0	0—10	Over 10	0	I	II	III	IV
Intraperitoneal injection of 1 ml 0.2% silver nitrate	64	26	10	20	80	80	80	40
Intraperitoneal injection of 1 ml silver nitrate + parmidine	80	13	7	30	70	70	60	20

TABLE 2. Distribution of Different Intensities of Labeling in Mesenteric Microvessels

Gradations of optical density on 10-point scale	Relative percentage of gradations of density in animals	
	with aseptic peritonitis	with aseptic peritonitis + parmidine
1*	14	4
2	12	11
3	16	14
4	21	24
5	37	47

*Corresponds to maximal intensity.

total area of deposition of colloidal carbon in the vessel wall to the total surface area of the mesenteric preparations examined. Parmidine was given internally in a dose of 50 mg/kg 60 min before injection of the ink.

EXPERIMENTAL RESULTS

Intravenous injection of adrenalin into mice led to an increase of almost 30% in the lung index, evidence of an increase in the weight of the lungs because of migration of the liquid part of the blood into the lung tissue. Parmidine in doses of 10 and 25 mg/kg reduced adrenalin edema by 16 and 27% respectively. A further increase in the dose of parmidine did not potentiate its action significantly (Fig. 1).

Intradermal injection of bradykinin and histamine caused an increase in microvascular permeability of the rat skin and the appearance of a blue stain at the sites of injection. In animals receiving parmidine in a dose of 10 mg/kg no change was observed in the diameter or intensity of staining of the papules compared with the control group. An increase in the dose of parmidine to 25 mg/kg led to a decrease in the action of bradykinin by about 50%. In a dose of 50 mg/kg, parmidine reduced the diameter of the stained papules at the site of injection of bradykinin by more than 60%. A further increase in the dose of parmidine to 100 mg/kg caused no increase in its inhibitory effect on the bradykinin-induced disturbance of skin capillary permeability (Fig. 2).

In all the doses used, parmidine had no effect on the disturbances of microvascular permeability induced by histamine, evidence of the selective antibradykinin direction of action of this substance.

In rats with aseptic peritonitis parmidine reduced both the intensity and the extent of disturbances of mesenteric microvascular permeability (Fig. 3, Table 1). Analysis of the mesenteric preparations by means of a television system showed that the maximal intensity of labeling (1st degree) in rats receiving parmidine was lower than in the control and, conversely, the minimal density of labeling (5th degree) was higher, evidence of a lower intensity of damage to the vessels (Table 2).

The extent of spread of lesions in the microvessels of the animals receiving parmidine also was less than in the control. For instance, coefficient K for these animals was $7.3 \cdot 10^{-5}$, compared with $14.6 \cdot 10^{-5}$ in the control, i.e., twice as high.

The experiments thus showed that parmidine reduces microvascular permeability in certain organs when increased as a result of simulation of various pathological states. This action of the drug can be attributed to its antibradykinin properties. For instance, in adrenalin-induced pulmonary edema in mice,

parmidine in a dose of 25 mg/kg reduced the intensity of the edematous response almost by one-third. These observations confirm the fact, established by Rothschild [12], that a component connected with activation of kinin formation and responsible for approximately one-third of the edematous response of the pulmonary microvessels is present in adrenalin-induced pulmonary edema.

In disturbances of capillary permeability in the skin induced by bradykinin and histamine, parmidine also had an inhibitory action, but only against the effects of bradykinin. These experiments confirmed previous observations made on a model of edema of the limb in rats, showing the selective antibradykinin action of parmidine and its inhibitory effect on the intensity of the exudative reaction in rats with peritonitis induced by silver nitrate [8, 9].

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