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The Protective Effect of Urinastatin in Patients with Ileus

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Summary. **The effect of the protease inhibitor urinastatin on serum granulocyte elastase was investigated in patients with ileus. Twenty patients who had developed adhesive ileus after abdominal surgery were divided into two groups; 10 received urinastatin while 10 patients did not. The nontreated group did not received a placebo. Serum granulocyte elastase concentration increased on admission of the ileus patient; its subsequent rate of decline increased in patients treated with urinastatin relative to those not treated. Urinastatin may thus prove clinically beneficial in the treatment of ileus, a condition that may result in bowel ischemia.**

INTRODUCTION

Conservative therapy for ileus has progressed with the use of treatments such as intravenous hyperalimentation, antibiotics and ileus tubes. However, ileus accompanied by bowel ischemic damage remains a serious problem. Recently, proteases have gained attention as possible mediators of ischemic damage in several organs.[1-3] Proteases increse capillary epithelial permeability and disturb the microcirculation;[4] granulocytes have been identified as a source of such mediators of toxicity.[5]

Protease inhibitors have been studied regarding the treatment of tissue injury.[1] The human urinary trypsin inhibitor, urinastatin, is an acidic glycoprotein with a molecular mass of approximately 67,000 daltons that has a potent inhibitory effect on the activities of trypsin and chymotrypsin.[6,7] Urinastatin also inhibits granulocyte elastase activity *in vitro*.[6] Granulocyte elastase in a neutrophilic protease that exhibits marked proteolytic activity. Urinastatin has proven effective in treating pancreatitis as well as traumatic, hemorrhagic and endotoxic shock.[6,8,9] We investigated the effect of urinastatin administration on serum granulocyte elastase in patients with ileus.

MATERIAL AND METHODS

From June 1992 to March 1993, conservative therapy was administered electively to 20 patients with adhesive ileus following abdominal surgery. All of the patients exhibited symptoms such as abdominal pain and nausea as well as niveau formation in abdominal radiographs.

These 20 patients were divided into two groups of 10 each. Only one group was intravenously treated with urinastatin (3×10^5 units/day) for 3 days after admission.

In the urinastatin treatment group, peripheral venous blood was collected before and 1 and 3 days after the initiation of urinastatin treatment. In the group not receiving urinastatin, blood was collected on admission and 1 and 3 days after admission, according to the same time course as that of the urinastatin group. Serum granulocyte elastase was measured with an enzyme-linked immunosorbent assay.[10] The addition of urinastatin to serum samples *in vitro* did not interfere with the assay of granulocyte elastase. Serum granulocyte elastase concentrations of 30 normal adults were determined during the same time period for comparison with the ileus patients.

All data are presented as means $\pm$ SD. Statistical analysis was performed with paired and nonpaired Student's t tests, and a p value of less than 0.05 was considered to be statistically significant.

RESULTS

A. Patient characteristics

The urinastatin treatment group comprised nine males and one female. Ages ranged from 24 to 84 years, with a mean of 59 $\pm$18 years. Ileus occurred

due to adhesions developing after abdominal surgery, which was performed for colon cancer in four patients, gastric cancer in four patients, cholecystolithiasis in one patient, and panperitonitis with perforated jejunum in one patient. In the conservative treatment for ileus, all patients received fluid nutrition in the form of lactated Ringer's solution: three patients were provided with nasal-gastric or ileus tubes. The group not treated with urinastatin contained eight males and two females. Ages ranged from 33 to 79 years, with a mean of 62 ±15 years. Ileus occurred due to adhesions developing after abdominal surgery performed for gastric cancer in six patients, colon cancer in three patients and duodenal ulcer in one patient. All patients received fluid nutrition: two patients were provided with nasal-gastric tubes.

The period from the beginning of conservative therapy to an observed reduction in niveau formation in abdominal radiographs was 2.8 ± 2.2 days in the urinastatin-treated group and 3.0 ± 1.9 days in the group not treated with urinastatin. Similarly, the period from the beginning of therapy to starting a solid diet was 3.2 ± 2.5 days and 3.3 ± 2.4 days in the two groups, respectively. Neither the niveau-diminishing period nor the diet-starting period differed significantly between the two groups.

All patients except one, who died of metastatic liver cancer, were discharged without complications.

B. Granulocyte elastase concentrations

The serum granulocyte elastase concentrations in the 30 normal adults was 73.3 ± 20.7 μg/l. The serum granulocyte elastase concentrations of the treatment and nontreatment groups were as follows: before starting urinastatin treatment or on admission to the nontreatment group, 212.7 ± 54.9 μg/l versus 210.5 ± 48.7 μg/l, respectively; one day after starting urinastatin treatment or 1 day after admission to the nontreatment group, 176.5 ± 40.6 μg/l versus 200.6 ± 50.8 μg/l ($p<0.01$); and 3 days after starting urinastatin treatment or 3 days after admission to the nontreatment group, 145.2 ± 24.6 μg/l versus 167.7 ± 38.7 μg/l ($p<0.01$) (Fig. 1).

The serum granulocyte elastase concentrations in both groups of ileus patients were significantly higher than those of normal adults ($p<0.01$). In the urinastatin treatment group, the granulocyte elastase concentration before the administration of urinastatin was significantly higher than the concentrations 1 and 3 days after the initiation of urinastatin treatment ($p<0.01$), and the concentration 1 day after the initial administration of urinastatin was significantly higher than that 3 days after starting urinastatin treatment ($p<0.01$) (Fig. 2).

In the nontreatment group, however, the serum granulocyte elastase concentration 1 day after admission to the group did not differ significantly from that on first admission: both of these concentrations were significantly higher than that measured 3 days after admission ($p<0.01$) (Fig. 3).

DISCUSSION

Granulocyte elastase, present in the azurophil granules of polymorphonuclear leukocytes, contributes to the degradation of phagocytosed material in these inflammatory tissue. Granulocytes may also directly release elastase in response to various stimulatory agents.[11] Several investigators have suggested that the excessive activity of this protease may disturb the function of endothelial cells and result in microcirculatory insufficiency and functional organ damage.[11,12] Studies have shown a correlation between granulocyte elastase concentration and the clinical prognosis of patients with sepsis and shock.[7,11,12]

The protease inhibitor urinastatin suppresses the extracellular release of free radicals that damage cellular membranes in ischemic organs.[1] Urinastatin has been used for the treatment of acute circulatory insufficiency and acute pancreatitis in Japan.[6,8] We have previously shown that urinastatin was successful in the treatment of ischemic bowel disease.[13] Generally, if ileus has occurred, bowel ischemic damage is advanced as a result of increased intraluminal pressure and excessive activity of neutrophils. Damage to cellular membranes and microcirculatory insufficiency would be expected to increase as a result of the activities of various agents including neutrophil proteases, free radicals, arachidonic acid metabolites and the platelet activating factor. We have now shown that serum granulocyte elastase concentrations increase in patients with adhesive ileus, and that urinastatin increases the rate of decline in elastase concentrations in such patients. Although we did not observe any overt clinical differences between patients who received urinastatin and those who did not, the treatment of ileus may benefit from the early pharmacological suppression of granulocyte elastase concentration with agents such as urinastatin.

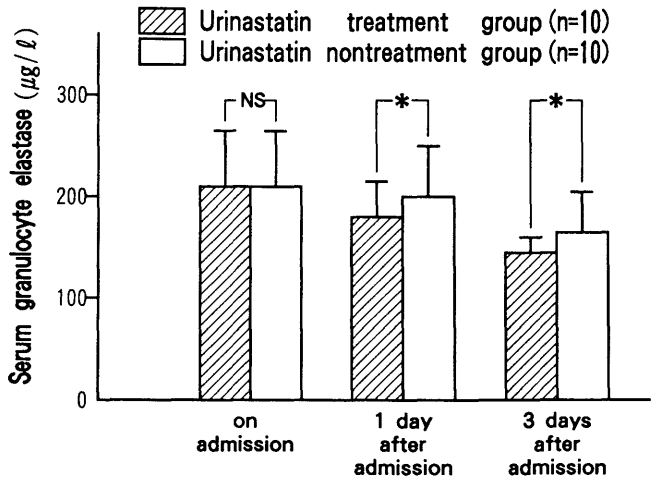

Fig. 1. Comparison of serum granulocyte elastase concentrations in ileus patients treated with urinastatin and those not treated with urinastatin. *p<0.01.

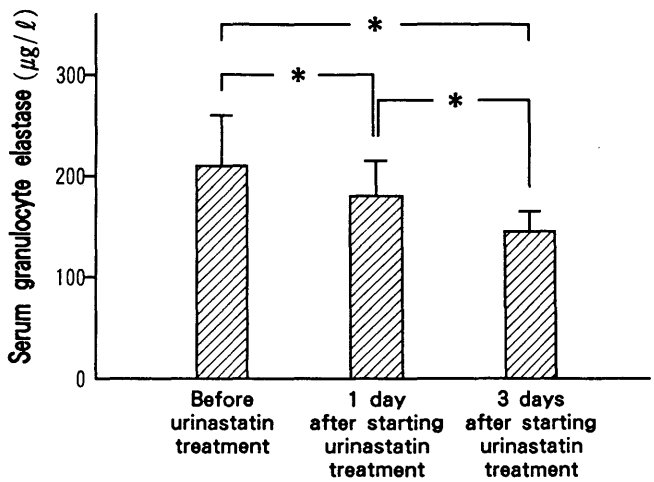

Fig. 2. Serum granulocyte elastase concentrations in ileus patients treated with urinastatin. Serum granulocyte elastase was measured in peripheral venous blood prior to, and 1 and 3 days after initial administration of urinastatin. *p<0.01.

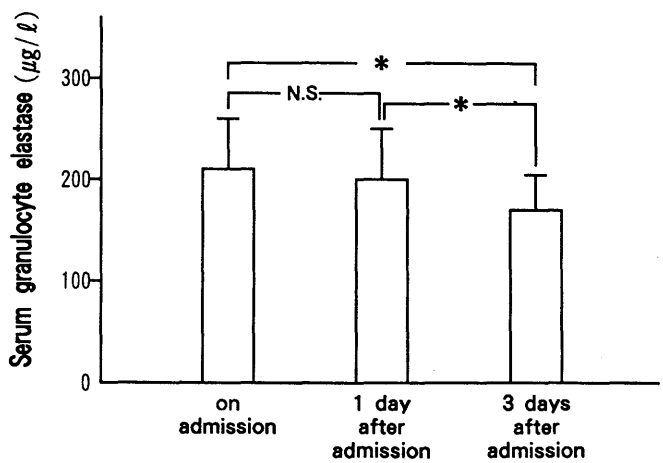

Fig. 3. Serum granulocyte elastase concentrations in ileus patients not treated with urinastatin. Serum granulocyte elastase was measured in peripheral venous blood on admission and 1 and 3 days after admission to the group. *p<0.01. N. S.: not significant.

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