EXPERIMENTAL AND CLINICAL STUDIES OF AN INHIBITOR OF TRYPSIN UPON ACUTE PANCREATITIS

The high-dose therapy and its effect upon renal disturbances associated with acute pancreatitis

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Introduction

Medical treatment for pancreatitis have been fairly substantially getting the better results in recent years. But, there is no definite therapy yet which may be regarded as the causative treatment for it. Polyvalent proteinase inhibitor (Trasylol) which has been developed by Frey\(^1\), and Werle\(^2\) et al. as an inhibitor of trypsin and kallikrein can be expected etiologically effective to acute pancreatitis for the following reasons. First, Trasylol is able to inhibit the action of trypsin, which plays an important role for the development and progress of acute pancreatitis. It is, therefore, expected that Trasylol prevents the progress of pancreatic lesions. Second, the conceivable action of Trasylol on pancreatic toxins is important. Patients with acute pancreatitis are not killed by the pancreatic lesions alone. Systemic toxic actions affect and damage the vital organs and tissues of the body, which greatly influences the course and prognosis of disease. Pancreatic toxins are composed of various factors. They can all be considered to be pancreatic enzymes and products decomposed by them. Tsukiyama et al.\(^3\) reported from their studies that the above mentioned toxins come mainly from the joint action of trypsin, lipase (including phospholipase) and amylase together with the decomposition products by these enzymes. Trypsin existing in vivo is by itself not so greatly damaging. When, however, lipase also appears and adds to trypsin, the toxicity rises very high. If the above two enzymes are joined by amylase, the joint toxicity is much higher. On the other hand, the damaging power of lipase and amylase without trypsin is not so strong so long as the concentrations of lipase and amylase are within an order as appears in vivo. If, therefore, the action of trypsin is inhibited by Trasylol, the damaging power of pancreatic toxins must be considerably lowered. This possibility makes us expect Trasylol to be effective. Third, as reported by Werle et al.\(^4\), in case of acute pancreatitis there are large amounts of kallikrein released into blood, which is conceivable to contribute to the development of shock. Inhibition of kallikrein activity by Trasylol, therefore, can be considered to work against shock.

For these reasons, Trasylol can be expected to be effective for acute pancreatitis. Although numerous workers have reported Trasylol effect, some others do not agree to it.

In this report, the effect of Trasylol on acute pancreatitis was studied. Primarily using Trasylol on experimental pancreatitis in the dog, the results were analysed by determining serum amylase, serum catalase, and blood sugar levels. Serum amylase is important for the diagnosis of pancreatitis, but its variations are not always parallel to the severity and course of pancreatitis. For this reason, serum
amylase alone does not suffice for the judgement. On the other hand Tsukiyama\(^6\), Kubota\(^5\), and Misumi et al.\(^6\) reported the elevation of serum catalase in acute pancreatitis and its variations, unlike those of serum amylase being closely parallel to the severity and clinical course of pancreatitis. This is the reason to determine serum catalase as the second basis for judging the effect.

Tsukiyama\(^7\) and Hoshida et al.\(^8\) reported that at the early period in acute pancreatitis the blood sugar levels are declined markedly, and that the degree of that decline show the severity of pancreatitis and predicts its prognosis. Blood sugar level is also determined as the third basis for the evaluation.

Based on these three factors: serum amylase, serum catalase, and blood sugar, the effectiveness of Trasylol on experimental pancreatitis was judged.

Subsequently, the effect of Trasylol was tested in 50 patients of acute pancreatitis. Exact judgement of the effectiveness is difficult in the case of acute pancreatitis which highly tends to run a self-limited course. The above judgement requires to set up definite standards in advance. Four items, analgesic effect, improvement in abdominal conditions, decline in serum amylase, and decline in serum catalase was employed.

I. Experimental studies:

Effect of Trasylol on experimental pancreatitis in the dog.

A. Experimental method:

It is necessary first of all to produce pancreatitis of a certain degree of severity for subsequent experiments. Surgical intervention was constantly limited to the minimum. By infusing, 0.1 ml of olive oil per kg of body weight into the pancreatic duct at a constant speed, pancreatitis of an approximately definite degree of severity was produced in all dogs. These dogs were divided into 3 groups; control, low-dose Trasylol, and high-dose Trasylol groups.

1) Control experiment:

Under anesthesia with Ravonal, the adult dog weighing 10 kg or so was laparotomized, and olive oil was infused via the duodenal orifice of the pancreatic duct major as mentioned above. Blood was withdrawn before operation, every 2 hours early after operation, and then every 6 to 24 hours.

2) Trasylol experiments:

The low-dose group was administered with Trasylol 4,000 K.I.U. immediately before operation and 2,000 K.I.U. each at 6 hours and 24 hours after operation and thereafter every 24 hours for 7 days.

The high-dose group was given Trasylol 50,000 K.I.U. immediately before operation and 10,000 K.I.U. each at 6 hours and 24 hours after operation and thereafter every 24 hours for 7 days. As the control, serum amylase, serum catalase, and blood sugar were determined in these two groups.

3) Serum amylase was measured by Somogyi's saccharogenic method\(^9\), serum catalase by the potassium permanganate method described by Inoue\(^10\), Ochi, and Shirai, and blood sugar by the Somogyi method.

B. Results:

Serum amylase in the control group was elevated to 1,036 to 3,579 units, averaging 2,047 units, and in the low-dose group to 613 to 1,231 units, averaging 944 units. Thus, the low-dose group showed less elevation than the control group. In the high-dose group, the serum amylase level was elevated to 260 to 724 units, averaging 472 units, which is less than in the control group and is evidently much less than in the low-dose group.