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Antiproteases in the Treatment of Acute Necrotizing Pancreatitis: Continuous Regional Arterial Infusion

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Summary

Acute necrotizing pancreatitis is still a fatal disease. Pancreatic necrosis might be, in part, a result of infarction due to ischemia with vasospasm and an increase in intravascular coagulability. Synthetic antiproteases have a broad inhibitory action on pancreatic enzymes, the coagulation system, the complement system and the production of proinflammatory cytokines. Therefore, antiproteases have been expected to prevent necrotic changes in the pancreas and to reduce the mortality rate. However, the clinical efficacy of antiproteases is still a matter of controversy. Unfortunately, an antiprotease cannot easily reach the pancreas when administered intravenously because of its pharmacokinetic characteristics and impaired microcirculation. Administration through a catheter placed in one of the arteries which supplies the inflamed area of the pancreas, dramatically increases the concentration of the antiprotease in the pancreas. Clinical studies of continuous regional arterial infusion of a protease inhibitor have been conducted in Japan and have demonstrated the possible therapeutic efficacy of the new treatment in severe acute pancreatitis.

Introduction

Severe acute pancreatitis is still a fatal disease. In particular, acute necrotizing pancreatitis is often associated with multiple organ failure and infected pancreatic necrosis resulting in a high mortality rate. An increase in intravascular coagulation and pancreatic ischemia associated with vasospasm may easily induce necrotic changes in the pancreas. Pancreatic necrosis might be, in part, a result of infarction due to pancreatic ischemia and the formation of a microthrombosis. Thrombin, which is markedly activated in severe acute pancreatitis, is considered to play an important role in vasospasm [1, 2]. In addition, thrombin upregulates intravascular coagulation with other promoting factors. Antiproteases have broad inhibitory actions on serine-proteases, the coagulation system, the complement system and the production of proinflammatory cytokines. Protease inhibitors, therefore, are expected to prevent necrotic changes in the pancreas and reduce the mortality rate. The efficacy of the synthetic protease inhibitor gabexate mesilate (FOY) was investigated in randomized controlled trials (RCTs) [3, 4, 5, 6, 7], but a meta-analysis [8] of four of them [3, 4, 5, 6] did not show a reduction in the mortality rate. However, the remaining RCT [7], published in 2000, showed that the continuous intravenous administration of FOY significantly reduced the frequency of complications and the mortality rate in patients with organ dysfunctions. Thus, the efficacy of antiproteases in severe acute pancreatitis is still a matter of controversy. Unfortunately, the antiproteases do not easily reach the pancreas when administered

intravenously because of their pharmacokinetic characteristics and impaired microcirculation. Administration through a catheter placed in one of the arteries which supplies the inflamed area of the pancreas dramatically increases the concentration of the antiprotease in the pancreas [9, 10, 11]. Clinical studies on the continuous regional arterial infusion (CRAI) of a protease inhibitor have been conducted in Japan and have demonstrated the possibile usefulness of a new regimen in severe acute pancreatitis. In this review, we discussed the possible therapeutic efficacy of the new treatment modality.

Ischemic Changes in the Pancreas Associated with Vasospasm in the Early Phase of Acute Necrotizing Pancreatitis

Severely impaired pancreatic blood flow due to vasospasm may be a major cause of pancreatic ischemia. Contrast-enhanced computed tomography (CECT) and angiography enabled us to observe that hypoperfusion of the pancreas and vasospasm occur concurrently in human acute necrotizing pancreatitis.

The angiographic appearances of arterial irregularities in acute pancreatitis have been described since the 1960s [12, 13, 14]. However, in this series, the main reason for angiography was the presence of complications, such as a palpable mass, an abscess, induration of the head of the pancreas or a pseudocyst. Unfortunately, angiography was performed at a late stage of the acute pancreatitis in most of the patients. In addition, the relationship between vasospasm and hypoperfusion of the pancreas detected on CECT in acute necrotizing pancreatitis has never been discussed in the literature.

Recently, the angiographic features of acute necrotizing pancreatitis were investigated in two Japanese medical centers using digital subtraction angiography with selective catheterization into the celiac and superior mesenteric arteries [15, 16, 17]. In the early phase of the disease, within one week after onset, various angiographic abnormalities were observed which were consistent with the location of the poorly perfused area of the pancreas found on CECT. Impaired filling of the pancreatic gland in the capillary phase and ischemic change with vasospasm were the most commonly observed in acute necrotizing pancreatitis. Narrowing, sudden tapering, and diffuse caliber irregularities of the intrapancreatic branch arteries were characteristic of acute necrotizing pancreatitis. Severe ischemic changes such as diffuse spasm and/or obstruction were found not only in the intra- and peri-pancreatic arteries, but also in the extrapancreatic arteries. On angiography, the extent of ischemic changes associated with vasospasm was correlated with the extent of the poorly perfused area of the pancreas and the severity of the acute pancreatitis.

Non-occlusive mesenteric ischemia (NOMI) associated with severe acute pancreatitis was also investigated based on the angiographic appearance of both the celiac and the superior mesenteric arteries [18, 19]. In patients with NOMI accompanied by acute necrotizing pancreatitis, severe vasospastic changes of both the celiac artery and the superior mesenteric artery were observed simultaneously. Diffuse narrowing of the common hepatic artery, the splenic artery and the intrapancreatic branch arteries were also observed. These findings suggest that severe ischemic changes in the intra-abdominal vessels may aggravate microcirculation not only in the pancreas but also in the abdominal viscera and may lead to multiple organ failure.

The mechanism of vasospasm has yet to be fully clarified. Hypovolemia, hypotension, and sympathetic stimulation are major causes of vasospasm. Local inflammation, endothelin, and the complement system may be other possible causes of vasospasm. Recently, endothelin has been proposed as a leading candidate for mediating the vascular sequelae of severe acute pancreatitis. Endothelin-1 (ET-1) is notably produced in severe acute pancreatitis [15]. ET-1 is stimulated by thrombin, and it induces vasospasm which may lead to pancreatic necrosis. Inoue *et al*. demonstrated that the

production of ET-1 by human umbilical vein endothelial cells (HUVECs) was significantly enhanced by the stimulation of thrombin, and that, in acute pancreatitis, a close relationship exists between ET-1 and vascular spasm [15]. Thrombin can activate ET, stimulating enzyme-1 to produce ET-1 via PAR-1 [20]. Thus, thrombin, which is noably activated in acute necrotizing pancreatitis, has been considered to play an important role in vasospasm along with proinflammatory cytokines. In acute necrotizing pancreatitis, hypovolemia and an increase in coagulability are commonly observed, and they are concomitant with vasospasm and pancreatic ischemia. Microcirculatory derangement due to the formation of microthrombosis in the pancreatic vessels and the evolution of ischemia into pancreatic necrosis may thus easily occur. Antiproteases have broad inhibitory actions on pancreatic enzymes, the coagulation system, the complement system and the production of proinflammatory cytokines. Nafamostat mesilate inhibits trypsin and phospholipase A2 which are major factors in causing pancreatic necrosis. It also inhibits the classical and alternative pathway of complement activation and the activation of thrombin, kallikrein and plasmin, factor VIIa and factor Xa [21, 22, 23]. Nafamostat suppresses activated thrombin and thereby inhibits the production of ET-1, thus preventing vasospasm and pancreatic necrosis. However, antiproteases administered intravenously may not reacha high enough concentration in pancreatic microcirculation. A high enough concentration of antiproteases can be achieved by CRAI, and antiproteases may improve or maintain local perfusion of the pancreas under conditions of pancreatic ischemia associated with vasospasm and increased coagulability in the early phase of acute necrotizing pancreatitis.

Concentrations of Protease Inhibitors in the Pancreas According to the Different Routes of Administration

Protease inhibitors are usually administered by intravenous infusion (mainly via central vein) in acute pancreatitis. However, most of the drug administered intravenously is delivered to the lung through the heart and then, to the liver or kidney. Therefore, only a small amount of the drug reaches the pancreas [24]. In addition, the half-life of a synthetic protease inhibitor is short. For example, the half-life of gabexate mesilate (FOY) is 55 seconds. In a German study [6], FOY at a dose of 4 g which was higher than that of a previous *in vitro* study was administered intravenously, but the clinical study did not show any beneficial effects on the mortality rate and the frequency of complications. However, are 4 g of FOY sufficient to prevent the progress of inflammatory change of the pancreas? There has been no reliable data indicating whether the dose of 4 g of FOY is optimal or not. A sufficient amount of FOY may not reach the pancreas when administered intravenously. If we apply a large amount of protease inhibitor intravenously to obtain a high concentration in the pancreas, the toxic effects to the liver and kidneys cannot be avoided.

In acute pancreatitis, CRAI, via one of the arteries which supplies the pancreas, is an effective drug delivery system for obtaining high concentrations of the drugs in the pancreas with minimal toxic effects. The concentration of a protease inhibitor in the pancreas according to the difference of infusion route has been investigated in some experimental studies [9, 10, 11]. In a canine experimental model treated with a synthetic protease inhibitor, nafamostat mesilate, the concentration of the drug in the pancreas was five times higher when administered intra-arterially than those infused intravenously [9]. Intra-arterial application of nafamostat reduced the trypsin-like activity in the pancreas and the extent of parenchymal necrosis of the pancreas significantly. In another canine experimental model treated with FOY, the concentration of FOY in the pancreas in the intra-arterial infusion group was 32 times greater than that in the intravenous infusion group [10]. The extent of pancreatic parenchymal necrosis in the intra-arterial infusion group was significantly

reduced as compared to the intravenous infusion group. The difference between nafamostat and FOY concentrations in the pancreas may be dependent on the difference of the half-life of the drugs (nafamostat 23 min *vs*. FOY 55 sec). In a rat experimental model treated with nafamostat, the concentrations of nafamostat in the pancreas after intra-arterial infusion was nine times higher than that after intravenous infusion [11]. However the CRAI rats had lower concentrations of nafamostat in the lungs than those infused intravenously. The CRAI of nafamostat significantly reduced the levels of trypsinogen activation peptide (TAP) and pancreatic necrosis. Moreover, the levels of IL-6 and the mortality rate were significantly reduced after CRAI as compared to the intravenous infusion of nafamostat.

Indication and Procedures of Continuous Regional Arterial Infusion (CRAI)

After the admission of a patient with acute pancreatitis, the severity is assessed according to the severity scoring system. Fluid resuscitation is mandatory in order to avoid hypovolemic shock or renal dysfunction. CECT is carried out on the day of admission. CRAI therapy is indicated for patients with acute necrotizing pancreatitis admitted within a few days after onset. After evaluating the location and the extent of the poorly perfused area of the pancreas, an angiography of the pancreas is performed. The femoral artery is punctured using the Seldinger method, and a 4F or 5F catheter is inserted into the femoral artery, and angiography via the celiac artery and superior mesenteric artery is performed. In CRAI therapy, it is important that the artery supplying the inflammatory region be selected as the route of administration. For example, if the main region of hypoperfusion of the pancreas is located in the pancreatic head, the tip of the catheter is placed at the common hepatic artery, the gastroduodenal artery or the superior mesenteric artery. If the main region of the hypoperfusion of the pancreas is located in the pancreatic body-tail, the tip of the catheter is placed at the splenic artery or the dorsal pancreatic artery. If the poorly perfused area extends to the entire pancreas, the tip of the catheter is placed at the celiac artery. The catheter for the infusion of the drugs is the same as that used for angiography. Nafamostat mesilate (240 mg) or gabexate mesilate (2,400 mg) dissolved in 500 mL of 5% glucose solution is infused through the catheter continuously at 20 mL/h. Imipenem (0.5 g) is dissolved in 100 mL saline and infused intra-arterially every 12 h. The period of CRAI therapy is 5 days, following which antibiotics are administered for 7 additional days in order to prevent pancreatic infection.

Clinical Aspect of CRAI Therapy in Severe Acute Pancreatitis

Clinical studies on the efficacy of CRAI therapy in severe acute pancreatitis have demonstrated excellent results [25, 26, 27, 28]. The high concentration of protease inhibitor in the pancreas obtained by CRAI may prevent necrotic changes in the pancreas and reduce the mortality rate. Anai *et al*. [29] evaluated the relationship between the therapeutic effect of CRAI therapy and drug distribution on CT-arteriography. In patients having a good drug distribution on CT-arteriography, there was a rapid decrease of the APACHE II score and the CT severity index by Balthazar. The CT severity index was 5-10 (mean, 7.9) before CRAI therapy, but it decreased to 0-3 (mean, 0.6). Hirota *et al*. also reported a case with NOMI associated with acute pancreatitis [18]. In that case, severe vasospasm occurred in both the celiac artery, the superior mesenteric artery and their branch arteries simultaneously. The patient received CRAI therapy with nafamostat solely via the celiac artery. The pancreas was spared from diffuse necrosis in contrast to the diffuse intestinal necrosis which occurred due to mesenteric vasospasm. We also investigated the effect of the CRAI of nafamostat and imipenem on the morphological changes of the pancreas by serial CECT examination in patients having a poorly perfused area of more than 30% on initial CT findings. CECT findings of the pancreas were examined on admission and 2 weeks after admission.

Morphological improvement (resolution or decrease of the extent of the poorly perfused area of the pancreas) was observed in 65.3% in patients with CRAI therapy whereas it was observed in only 18.8% in patients with non-CRAI therapy.

However, pancreatic infection, especially infected pancreatic necrosis, is also a crucial factor of death in acute necrotizing pancreatitis. We conducted a pilot study of CRAI therapy in acute necrotizing pancreatitis in 1988. CRAI of the protease inhibitor nafamostat decreased the mortality rate in acute necrotizing pancreatitis, but did not reduce the frequency of pancreatic infection (infected pancreatic necrosis and pancreatic abscess). Therefore, we have been trying a new regimen of CRAI therapy in which both protease inhibitor and antibiotic were infused simultaneously via the same route supplying the inflamed area of the pancreas since 1992. CRAI of both the protease inhibitor and the antibiotic reduced not only the mortality rate but also the frequency of pancreatic infection [25]. Hayashi *et al*. also confirmed the efficacy of intra-arterial antibiotic infusion in preventing pancreatic infection in a canine model of acute necrotizing pancreatitis [30]. The concentration of antibiotic in the pancreas was significantly higher in the intra-arterial infusion group than that in the intravenous infusion group. Continuous intra-arterial infusion of antibiotic completely prevented the occurrence of pancreatic infection, and improved the survival rate. A nationwide survey of CRAI therapy in acute necrotizing pancreatitis in Japan also demonstrated that CRAI of both the protease inhibitor and the antibiotic was superior to CRAI of the protease inhibitor alone [26]. There was no significant difference in mortality rate between patients who received the protease inhibitor via CRAI and the antibiotic intravenously, and patients who received both the protease inhibitor and antibiotic via CRAI, but the frequency of infected pancreatic necrosis was significantly lower in patients with CRAI involving both drugs than in patients with CRAI involving protease inhibitor alone.

The therapeutic window of CRAI therapy is narrow. CRAI therapy should be initiated as soon as possible after diagnosing acute necrotizing pancreatitis by CECT, because pancreatic necrosis is established within 4-5 days after the onset. We evaluated the effect of the timing of initiation of CRAI therapy on the outcome of patients with acute necrotizing pancreatitis [27]. The frequency of respiratory failure requiring mechanical ventilation was low in patients in whom CRAI therapy was initiated within 72 h after the onset as compared to that in patients in whom CRAI was initiated more than 72 h after the onset. The mortality rate was also significantly lower in patients in whom CRAI therapy was initiated within 72 h after onset. A nationwide survey of CRAI therapy in acute necrotizing pancreatitis also demonstrated that the mortality rate was lower in patients in whom CRAI therapy was initiated within 48 h after the onset as compared to that in patients in whom CRAI was initiated more than 48 h after the onset [26]. We investigated the timing of the initiation of CRAI therapy and the morphological changes found on serial CECT findings [31]. Morphological improvement was observed in 84% of the patients in whom CRAI was initiated within 48 h after the onset, whereas it was observed in only 53% of the patients in whom CRAI was initiated more than 72 h after the onset.

Conclusion

Pancreatic ischemia and upregulation of intravascular coagulation play a crucial role in the derangement of microcirculation and the development of pancreatic necrosis. A high enough concentration of antiprotease obtained by CRAI may prevent necrotic changes in the pancreas by the suppression of pancreatic ischemia associated with vasospasm and the inhibition of an increase in the coagulability of the pancreatic microcirculation. Experimental and clinical evidence supported the possible usefulness of CRAI therapy; however, further evidence is needed to establish the specific therapy required for the management of severe acute pancreatitis.

Keywords FOY 305; Gabexate; Infusions, Intra-Arterial; Ischemia; nafamostat; Pancreatitis, Acute Necrotizing; Protease Inhibitors; Vasoconstriction

Abbreviations CRAI: continuous regional arterial infusion; ET-1: endothelin-1; HUVEC: Human umbilical vein endothelial cells; NOMI: non-occlusive mesenteric ischemia; RCT: randomized controlled trial; SMA: superior mesenteric artery

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