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Antiproteases in the Treatment of Acute Pancreatitis

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Introduction

The pathogenesis of acute pancreatitis relates to the inappropriate activation of trypsinogen to trypsin and a lack of the prompt elimination of the active trypsin inside the pancreas. Therefore, trypsin is believed to be the key enzyme in the initiation and exacerbation of acute pancreatitis by activating pancreatic zymogens. The activation of digestive enzymes causes pancreatic injury and results in an inflammatory response. The acute inflammatory response in the pancreas induces the systemic production of cytokines causing substantial tissue damage, and may progress beyond the pancreas to a systemic inflammatory response syndrome (SIRS), multi-organ failure (MOF) or death [1].

In several studies, protease inhibitors have not been shown to be of significant value in the treatment of acute pancreatitis and are not available in the United States [2]. Several guidelines [3, 4, 5, 6, 7, 8, 9, 10, 11, 12] on the treatment of acute pancreatitis do not recommend them and the debate about the use of protease inhibitors is mentioned. On the other hand, several studies on prophylaxis with protease inhibitors for pancreatitis induced by endoscopic retrograde cholangiopancreatography (ERCP) have recently revealed their favorable effects in preventing serum pancreatic enzyme elevation, abdominal pain or the onset of pancreatitis [13, 14, 15, 16, 17, 18, 19, 20, 21]. Also, several meta-analyses have shown

that gabexate mesilate significantly reduced the complications of acute pancreatitis, such as sepsis and bleeding [22, 23].

In the present review, we discuss the current consensus on the treatment of acute pancreatitis with protease inhibitors and also whether treatment with protease inhibitors decreases the morbidity and mortality rates resulting from acute pancreatitis.

Do Protease Inhibitors Decrease Morbidity or Mortality of Patients with Acute Pancreatitis?

Despite strong experimental evidence, protease inhibitors have still not been proven to have favorable effects in the prognosis and clinical course of acute pancreatitis. There are several guidelines for the treatment of acute pancreatitis, deriving from an extensive review of the literature [3, 4, 5, 6, 7, 8, 9, 10, 11, 12]. In almost all the guidelines, the use of protease inhibitors is not recommended for the treatment of patients with acute pancreatitis. Only Japanese [6] and Chinese guidelines [11] recommend the routine use of gabexate mesilate in severe acute pancreatitis. In the Japanese guidelines, a continuous infusion of high doses of gabexate mesilate does not affect mortality, but significantly reduces both the incidence of complications in general and those requiring surgery. In the Chinese guidelines for acute pancreatitis, protease inhibitors should be given early and in sufficient dosages if needed.

Despite the considerable experimental data to

support the use of protease inhibitors in acute pancreatitis, a number of clinical trials have failed to show any benefits. Some reasons for this discrepancy have been proposed: 1) unlike the animal models where protease inhibitors are given at the time of induction of acute pancreatitis, patients present to a hospital too late to benefit from their administration; 2) unlike *in vitro*, *in vivo* gabexate mesilate has a T1/2 of less than 1 minute and its complexes with trypsin rapidly dissociate, so a continuous intravenous infusion of a high dose of gabexate needs to have its efficacy *in vivo*; 3) intrapancreatic levels are difficult to assess because absorption into the inflamed pancreas by the intravenous administration of protease inhibitors is questionable.

Several meta-analyses of the randomized controlled trials have demonstrated the favorable effects of gabexate mesilate in the prophylaxis of ERCP-induced pancreatitis and the treatment of acute pancreatitis [22, 23]. Seta *et al.* [22], in a recently published meta-analysis of protease inhibitors in acute pancreatitis, evaluated placebo-controlled randomized control trials of intravenously administered protease inhibitors in the treatment of acute pancreatitis. They concluded that treatment using protease inhibitors for acute pancreatitis did not influence overall mortality, pseudocyst formation, pancreatic abscess or the need for surgical treatment; however, in trials with patients having moderate to severe pancreatitis (control mortality rate (CMR) greater than 10%), protease inhibitors reduced mortality (pooled risk difference: -0.07; 95% CI from -0.13 to -0.01) which was significant (vs. placebo treatment) according to meta-regression analysis (P=0.017). In the discussion, they comment that a CMR greater than 10% was similar to mortality in patients having an APACHE II score of 6 and equivalent to a patient with high-grade fever, leukocytosis, acidosis, hyperventilation and losing consciousness.

Heinrich S *et al.* [12] performed a meta-analysis on the trials of Buchler *et al.* [24] and Chen *et al.* [25]. Neither the need for surgery

nor the mortality rates were significantly reduced by gabexate treatment. From this analysis, they concluded that gabexate mesilate does not improve the outcome of patients with severe pancreatitis, and its routine use in patients with severe pancreatitis is not recommended.

In a meta-analysis by Andriulli *et al.* [26], neither somatostatin, octreotide or gabexate proved to be of value in mild pancreatitis. In severe pancreatitis, both somatostatin and octreotide were beneficial in improving the overall mortality rate; the odds ratios (ORs) were 0.36 (95% CI: 0.20-0.64, P=0.001) and 0.57 (95% CI: 0.35-0.88, P=0.006), respectively.

The results of a meta-analysis by Messori *et al.* [23] indicate that treatment with gabexate mesilate does not affect mortality at 90 days (P=0.27), but significantly reduces the incidence of complications requiring surgery (OR=0.61, 95% CI: 0.41-0.89; P<0.05) and of complications in general (OR=0.69, 95% CI: 0.54-0.89; P<0.05). Since the drug is beneficial only to a low proportion of the patients treated, its clinical impact seems to be small. A pharmacoeconomic evaluation shows that its use in all patients with acute pancreatitis would involve a very high cost for preventing each complication. The administration of the drug to select patients who are at higher risk of complications may have a better cost-effectiveness ratio.

In the 1960s, the protease inhibitor aprotinin was widely used for patients with acute pancreatitis, but controlled studies have not confirmed the effectiveness of the drug. One double-blind randomized trial [27] compared intraperitoneal aprotinin versus saline application, and one randomized study compared intravenous aprotinin *versus* gabexate mesilate [28]. No difference was detected between intraperitoneal aprotinin and the control group except for the need for surgery, which was defined as symptomatic necrosis and persisting organ failure. In addition, intravenous aprotinin was significantly less effective than gabexate mesilate regarding the systemic complication rate and the need for surgery. Neither

intraperitoneal nor intravenous aprotinin improve the outcome of patients with severe acute pancreatitis; therefore, its routine use in patients with severe acute pancreatitis is not recommended [12].

How Are Protease Inhibitors Used for the Treatment of Acute Pancreatitis in Japan?

In 2003, the Japanese Society for Abdominal Emergency Medicine, the Japan Pancreas Society and the Research Committee of Intractable Diseases of the Pancreas supported by the Japanese Ministry of Health, Labor, and Welfare published "Evidence-Based Clinical Practice Guideline for Acute Pancreatitis" [6] which was revised in 2007.

In the Japanese guidelines, the continuous infusion of high doses of gabexate mesilate does not affect mortality, but significantly reduces the incidence of complications in general and those requiring surgery. Therefore, gabexate mesilate is recommended in severe pancreatitis.

The effect of protease inhibitors is controversial; experts on pancreatitis in Japan [29] recommend administering protease inhibitors as soon as the diagnosis of acute pancreatitis is confirmed. Otsuki *et al.* [29] reviewed the appropriate timing and doses of protease inhibitors used for acute pancreatitis in Japan. The usual doses of gabexate mesilate (FOY), nafamostat mesilate (FUT) and ulinastatin (UTI) for acute pancreatitis are 200-600 mg/day, 10-60 mg/day and 50,000-150,000 units/day, respectively. However, since severe acute pancreatitis is often complicated by disseminated intravascular coagulation and shock, it is recommended that these reagents be given in doses approved for these disorders in severe acute pancreatitis (FOY: 30-40 mg/kg/day; FUT: 2.4-4.8 mg/kg/day; UTI 5,000-10,000 units/kg/day) [30]. Combination therapy with FOY or FUT together with UTI is recommended when severe pancreatitis is predicted [30].

Are Protease Inhibitors Effective for the Prevention of ERCP-Induced Pancreatitis?

There are several reports demonstrating that protease inhibitors are effective in preventing

ERCP-induced pancreatitis if administered prior to the procedure [12, 13, 14, 15, 16, 17, 18, 19, 20, 21]. To prevent the occurrence of post-ERCP pancreatitis, the administration of several types of drugs has been investigated and gabexate mesilate was clearly shown to have a preventative effect against the development of post-ERCP pancreatitis in a large-scale prospective randomized double-blind study [18, 19, 20]. Cavallini *et al.* [18] reported that an infusion of a high dose of gabexate mesilate (1000 mg/12 h) provided a statistically significant protective effect. More recently, a meta-analysis reported by Andriulli *et al.* [13, 14] clarified that the administration of high-dose gabexate, as well as of somatostatin, prevented the occurrence of post-ERCP pancreatitis. Therefore, high-dose gabexate administration has become widely accepted as a preventative measure for post-ERCP pancreatitis, although the disadvantages of that therapy are the necessity for continuous infusion and vascular pain caused by the drug.

On the other hand, there are conflicting opinions concerning the routine use of gabexate as a prophylaxis for pancreatitis induced by ERCP [31]. Whitcomb [2, 32] mentioned that the use of prolonged infusions for pharmacologic prophylaxis against severe pancreatitis after ERCP is more expensive than the use of pancreatic stents in high-risk patients.

Testoni *et al.* [21] evaluated the frequency of post-ERCP pancreatitis and costs in a series of consecutive patients who have undergone ERCP procedures before and after the introduction of a routine prophylaxis with gabexate in all cases. The frequency of pancreatitis appeared significantly reduced in the gabexate period in comparison to the pre-gabexate period overall (2.2% *versus* 3.9%; $P=0.019$); however, the reduction was significant only in high-risk patients (3.8% *versus* 7.3%; $P=0.001$) on the basis of patient- and technique-related risk factors. Hyperamylasemia at 4-6 h and 24 h after the procedure was also significantly reduced only in high-risk patients ($P=0.001$). They concluded that routine gabexate prophylaxis

was associated with a significant reduction in the post-ERCP pancreatitis rate, hyperamylasemia and hospitalization-related costs only in high-risk patients.

Tsujino *et al.* [33] assessed the efficacy of ulinastatin (formerly urinastatin), a high molecular weight protease inhibitor derived from human urine, for the prevention of post-ERCP pancreatitis and hyperamylasemia. In a multicenter, randomized, double-blind, placebo-controlled trial, patients undergoing ERCP were randomized to receive ulinastatin (150,000 units) or a placebo by intravenous infusion for 10 minutes, starting immediately before ERCP. The incidence of hyperamylasemia was significantly lower in the ulinastatin group than in the placebo group. Six patients in the ulinastatin group and 15 patients in the placebo group developed pancreatitis (2.9% vs. 7.4%, $P=0.041$). There was no case of severe pancreatitis in either group. Prophylactic short-term administration of ulinastatin decreases the incidence of pancreatitis and hyperamylasemia after ERCP.

Fujishiro *et al.* [34] investigated the preventive effect of ulinastatin on post-ERCP pancreatitis, as compared to gabexate. Patients undergoing ERCP were randomly divided into three groups based on the agent and the dose given during and following the ERCP procedure: gabexate mesilate (900 mg), high-dose ulinastatin (450,000 units) and low-dose ulinastatin (150,000 units). Serum amylase, interleukin-6 (IL-6) and IL-8 levels and plasma polymorphonuclear leukocyte elastase (PMN-E) activity were measured after ERCP. There were no significant differences in serum amylase and cytokine activity after ERCP procedure between the three groups. Post-ERCP pancreatitis was observed in two (4.3%), three (6.5%), and four (8.5%) cases in the gabexate mesilate, high-dose ulinastatin, and low-dose ulinastatin groups, respectively. Multiple logistic regression analysis showed that the addition of endoscopic sphincterotomy during the ERCP procedure was the only significant risk factor for the development of post-ERCP hyperamylasemia and post-ERCP pancreatitis

($P=0.03$ and $P=0.04$, respectively), but there was no significant difference in the occurrence of post-ERCP hyperamylasemia and post-ERCP pancreatitis among the three groups. The administration of low- and high-dose ulinastatin has similar effects to high-dose gabexate in the prevention of post-ERCP pancreatitis.

Famulano *et al.* [2] presented their opinion about the prophylactic administration of gabexate for post-ERCP pancreatitis. Studies of the pharmacologic prevention of pancreatitis after ERCP have had disappointing results, except for those involving gabexate which has consistently shown a clinically appreciable effect in this setting. One important adverse aspect of gabexate has been the need to administer the drug by continuous infusion for about 12 hours, which renders this strategy not cost-effective. However, infusions lasting 6.5 hours have been shown to be as effective as longer infusions, with evident cost savings.

Continuous Regional Arterial Infusion of Protease Inhibitors and Antibiotics

Protease inhibitors were not so effective as expected because of the timing of the administration, the concentration of the protease inhibitor in pancreatic tissue and the diminution of the vasculature of the pancreas. To increase the concentration of the protease inhibitor, the arterial infusion of protease inhibitors was tried in acute necrotizing pancreatitis [29, 35].

The concentration of protease inhibitors and antibiotics in pancreatic tissue after continuous regional arterial infusion (CRAI) were proven to be approximately 5 and 5-10 times [36, 37] higher, respectively, than when the drug was infused intravenously. Also, intrapancreatic gabexate mesilate levels achieved by an intra-arterial route are 32 times higher than after intravenous administration of the same dose in experimental acute pancreatitis in dogs [38]. Intra-arterial administration may reach the effective concentration for inhibiting activated trypsin, and provide locally high

concentrations while minimizing systemic side effects.

Takeda *et al.* [35] reported the usefulness of CRAI of both the protease inhibitor nafamostat and the antibiotic imipenem in reducing the mortality rate and the frequency of infected pancreatic necrosis. A multicenter trial in Japan, conducted by Takeda *et al.* [39], reported the usefulness of the CRAI of protease inhibitors and antibiotics in 156 patients with acute necrotizing pancreatitis collected in a cooperative survey carried out in 1997. The overall mortality rate was 18.6%, and the frequency of infected pancreatic necrosis was 12.8%. There was no significant difference in mortality rates between patients who received the protease inhibitor via CRAI and the antibiotics intravenously (Group A) and patients who received both the protease inhibitor and the antibiotics via CRAI (Group B), but the frequency of infected pancreatic necrosis was significantly lower in Group B (7.6%) than in Group A (23.5%). The mortality rate in patients in whom CRAI therapy was initiated within 48 h after the onset of acute necrotizing pancreatitis (11.9%) was significantly lower than that in patients in whom CRAI therapy was initiated more than 48 h after onset (23.6%). These results suggested that CRAI of both protease inhibitors and antibiotics was effective in reducing mortality and preventing the development of pancreatic infection in acute necrotizing pancreatitis when initiated within 48 h after the onset of pancreatitis.

Either nafamostat or gabexate is used for this procedure because these agents are synthetic low-molecular-weight protease inhibitors. In addition, gabexate and nafamostat might easily penetrate into the pancreatic acinar cells due to their low molecular weight and inhibit the inflammatory process in the pancreas.

Antiproteases and Non-Occlusive Mesenteric Ischemia (NOMI) in Acute Pancreatitis

Many factors may be involved in the development of pancreatic ischemia in severe

acute pancreatitis [40]. NOMI has been defined as diffuse intestinal ischemia which often results in intestinal gangrene in the presence of a patent arterial trunk. Acute pancreatitis associated with NOMI was proven to be extremely severe. The prevalence and nature of NOMI in acute pancreatitis has been investigated. The mechanism of vasospasm has not been 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 spasm. Yanamoto *et al.* [41] demonstrated the therapeutic effect of the synthetic serine protease inhibitor, nafamostat, on cerebral vasospasm after subarachnoid hemorrhage. In patients treated with higher doses of nafamostat, there was no spasm or only mild vasospasm on angiogram. It has been suggested that the preventative effect of nafamostat may be the result of inhibition of the complement system.

Hirota *et al.* [42] reported a patient with NOMI associated with acute pancreatitis. Their patient received CRAI therapy with nafamostat solely via the celiac artery. The pancreas was spared from diffuse necrosis in contrast to diffuse intestinal necrosis which occurred due to mesenteric vasospasm. In some patients with spastic changes in both the celiac artery and the superior mesenteric artery, the development of intestinal necrosis was inhibited by performing CRAI with nafamostat via both arteries.

Conclusion

There is no concrete evidence to justify the routine use of protease inhibitors against acute pancreatitis. Continuous intravenous administration of high-dose protease inhibitors and continuous regional arterial infusion of protease inhibitors and antibiotics seem to be effective in preventing the exacerbation of severe acute pancreatitis. However, further research is needed to evaluate their cost-effectiveness. There are several reports demonstrating that protease inhibitors are effective in preventing ERCP-induced pancreatitis, if administered prior to

the procedure. It is unclear whether all patients undergoing ERCP would benefit from the use of protease inhibitors or only those who are at greater risk for pancreatitis.

Keywords Cholangiopancreatography, Endoscopic Retrograde; Gabexate; nafamostat; Pancreatitis, Acute Necrotizing; Protease Inhibitors; urinastatin

Abbreviations CMR: control mortality rate; CRAI: continuous regional arterial infusion; NOMI non-occlusive mesenteric ischemia

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