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Antiproteasic Agents in the Prevention of Post-ERCP Pancreatitis: Rationale for Use and Clinical Results

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Experimental Evidence: "How Acute Pancreatitis Begins and Evolves"

Acute pancreatitis is an inflammatory disease of the pancreas which may involve several organs with the onset of systemic complications. Recently, much progress has been made in understanding the pathogenesis of acute pancreatitis and the mechanisms for the onset of local and systemic complications [1, 2, 3]. However, in both animal models and in humans, it is not yet completely understood and is, therefore, still controversial [4].

Since 1896, acute pancreatitis has been considered the clinical manifestation of an autodigestive disorder of the pancreas [5] in which the pancreatic tissue is destroyed by its own digestive enzymes. There is general agreement that the inappropriate activation of trypsin is the initial event in the pathogenesis of acute pancreatitis [1, 2, 3, 4, 6]. Physiologically, pancreatic enzymes are synthesized as inactive precursors, packed into zymogens, secreted in the acinar lumen, transported by the pancreatic ductal system into the duodenum and finally activated in the duodenal lumen by an enterokinase. Trypsinogen is the first enzyme activated and, subsequently, it transforms all the other pro-enzymes to their respective active forms.

A disturbance of the normal secretion process in pancreatic acinar cells has been considered to be the initial event in the pathogenesis of acute pancreatitis. In many experimental animal models of acute pancreatitis, such as supramaximal stimulation of cerulein [1, 7], choline-deficient ethionin (CDE) enriched diet [8] and obstruction of the pancreatic duct [9, 10], a block of the physiological secretion of zymogens into the acinar lumen has been demonstrated. Therefore, the digestive enzymes and lysosomal hydrolase seem to migrate into the basolateral part of the acinar cells. A consequence of this "co-localization" is the dangerous contact between pancreatic pro-enzymes and lysosomal hydrolases, enzymes that may activate trypsinogen into trypsin. Cathepsin B, a lysosomal cystein proteinase, probably plays a central role in trypsin activation because it may activate trypsinogen in vitro [11, 12] and, in the very early phases of acute pancreatitis, it is localized in granules containing pancreatic enzymes [13]. Furthermore, there is experimental evidence that the inhibition of cathepsin B prevents trypsinogen activation and reduces the severity of acute pancreatitis [14] and, in mice in which the gene codifying for cathepsin B was deleted by targeted disruption (*ctsb*$^{-/-}$), the trypsin activation after the induction of experimental secretagogue-induced pancreatitis was more than 80% lower than in *ctsb*$^{+/+}$ mice [15].

In experimental acute pancreatitis in rats, an accumulation of trypsinogen in the interstitial space and its activation may transform a mild edematous pancreatitis into severe necrotizing pancreatitis [3].

Once the acute pancreatitis is initiated within the pancreas, other mechanisms are involved in the progression of the disease and in the onset of local and systemic complications.

The distal organ damage is initially mediated by activated pancreatic enzymes (trypsin,

phospholipase A and elastase) [16, 17, 18], but there is experimental evidence that many inflammatory mediators released from the inflamed pancreas are implicated in the onset of multi-organ failure (MOF) [19, 20, 21]. After trypsinogen activation to trypsin, local pancreatic damage results in the activation of inflammatory cells (neutrophils, macrophages, lymphocytes) and in the local production of inflammatory mediators (TNF-α, IL-1, IL-6, IL-8). This process amplifies local pancreatic damage and, when these mediators pass into the circulation, they may also amplify the inflammatory damage in other organs (lung, kidney, liver, heart, etc.). Cytokines may also activate the endothelial cells and facilitate the trans-endothelial migration of inflammatory cells into the pancreas and other organs, where they accumulate and amplify the inflammatory process [21].

In patients affected by severe acute pancreatitis, a second inflammatory insult, such as a "line" infection or chest infection, adds a second source of inflammatory mediators, amplifies the systemic inflammatory response syndrome (SIRS) and may lead to death (two-hit hypothesis) [21, 22].

In those patients who die as a result of severe acute pancreatitis, a large part (60%) of the deaths occur in the first week as the result of an exaggerated systemic inflammatory response related to sterile necrosis (sterile MOF). The remaining 40% of the patients die in the 3rd–4th week from the onset of infection of the necrotic tissue which leads to sepsis and multi-organ failure (infected MOF) [21].

Antiproteases and Acute Pancreatitis: Results of Experimental Studies

The discovery of new low molecular weight drugs having a potent and broad antiproteasic action (gabexate, nafamostate, camostate) in the 70s along with new experimental models of acute pancreatitis, resulted in a large number of studies which tried to demonstrate the efficacy of the new antiproteases in therapy and prevention of experimental acute pancreatitis.

Antiproteases are effective in different models of acute pancreatitis, such as pancreatitis induced by a CDE supplemented diet [23, 24, 25, 26], by hyperstimulation with cerulein or cholecystokinin [24, 26, 27, 28], by intraductal injection of sodium taurocholate [29, 30, 31, 32] or bile [33] or by a closed duodenal loop [34, 35].

The efficacy of antiproteases in experimental acute pancreatitis has been demonstrated in every type of administration: intravenous [24, 27, 28, 29, 32], intraduodenal [34, 35], intraductal [31], intraperitoneal [25, 30, 33], subcutaneous [23] or oral [24, 26].

The results in the use of antiproteases during experimental acute pancreatitis have pointed out many aspects which should be addressed in clinical research on humans.

First of all, antiproteases are effective if their dosage is appropriate. In acute pancreatitis induced in rats by intraductal injection of sodium taurocholate, Leonhardt *et al*. [30] demonstrated that the intraperitoneal administration of camostate reduced the mortality of the treated animal only at high dosages, whereas it was comparable to a placebo group at low dosages. Secondly, the time of administration of the drug is also important. Lankisch *et al*. [29] demonstrated that, in acute pancreatitis induced in rats by intra-ductal injection of sodium taurocholate, the administration of camostate before the induction of pancreatitis (prevention of the disease) is able to significantly improve the survival of the treated animals. After the induction of pancreatitis (therapy of the disease), the sooner camostate is administered, the more effective it is. If the administration of camostate is very delayed (more than 60 minutes after the induction of pancreatitis), the survival rate in the treated group is similar to that observed in the placebo group.

Experimental studies have also demonstrated that antiproteases may potentially act in several ways to prevent or block the development of acute pancreatitis:

1. by preventing intracellular events which lead to the inappropriate intracellular activation of trypsin;
2. by preventing extra-cellular events, such as the interstitial activation of trypsin;
3. by inhibiting inappropriately activated pancreatic enzymes, particularly trypsin;
4. by reducing the activation of macrophages, monocytes and polymorphonuclear cells in the necrotic pancreatic tissue;
5. by inhibiting the release of cytokines, free radicals and other biologically active mediators, which might amplify and export the inflammatory process from the activated inflammatory cells into the circulation and to other organs;
6. by inhibiting the trans-endothelial migration of the inflammatory cells, probably by a reduction of the intercellular adhesion molecule-1 (ICAM-1) and endothelial leucocyte adhesion molecule-1 (ELAM-1) expression on the endothelial cells and, consequently, a reduction of the adhesion of inflammatory cells on the endothelial cells.

Gabexate mesilate (ethyl-guanidine-hexanoil-oxy-dibenzoate-methyl-sodium-sulfonate), in particular, is a synthetic protease inhibitor of 417 daltons which is not antigenic and diffuses easily. Gabexate inhibits trypsin, kallikrein, plasmin (even when bound to alpha$_2$-macroglobulin), thrombin (even in the absence of antithrombin III), phospholipase A_2 and also C1 esterase [36]. Since it has a low molecular weight, gabexate may easily diffuse into the pancreatic acinar cells, prevent colocalization, probably by inhibition of an esterase [24], and control intracellular activation of trypsinogen. It may also inhibit trypsin inappropriately activated into the acinar cells and in the interstitial space [3], and may furthermore block other proteases eventually activated "a cascade" from trypsin. In the presence of a more advanced stage, such as in the presence of necrosis, gabexate limits the pancreatic damage by inhibition of the activated pancreatic enzymes and their release from the pancreatic necrotic tissue into the circulation, with a lower activation "in loco" and in the circulation of the macrophages, monocytes and polymorphonuclear cells. Gabexate limits the release of inflammatory cytokines (e.g. TNF-α, IL-6, and IFN-α) from activated inflammatory cells [37, 38, 39, 40, 41, 42, 43, 44, 45] and, therefore, reduces a further activation of inflammatory cells locally, in the circulation and in distal target organs, with a reduction of the systemic inflammatory response syndrome and multi-organ failure. Finally, there is experimental evidence that gabexate reduces the production of free radicals from leukocytes and macrophages and, consequently, the endothelial and tissutal damage mediated by oxidative stress [39, 43] and the production of NO by an inhibition of nitric oxide synthase (NOS) I and III enzymes [43].

In summary, experimental studies seem to clearly demonstrate that gabexate may prevent the onset of acute pancreatitis by interfering with the intracellular events that lead to the disease, may limit pancreatic damage after the onset of acute pancreatitis and may reduce the systemic complications, therefore reducing the morbidity and mortality of the disease.

Antiproteases and Acute Pancreatitis: Results of Clinical Studies

The first studies on the use of gabexate in human acute pancreatitis appeared in the Japanese literature towards the end of 70s. These studies involved a large number of patients but the experimental protocols were not correct (non-controlled trials, contemporary use of other drugs, inadequate dosage, incorrect time of administration, stratification of patients) and they cannot permit us to draw any conclusions. However, these trials documented a very low incidence of side effects and, therefore, the safety of the clinical use of gabexate mesilate.

In the 80s and 90s, many papers were published in the literature with apparently conflicting results. The first clinical trials [44, 45, 46], controlled vs. placebo or conventional treatment, concluded that

treatment with gabexate reduces the complications of acute pancreatitis, the need for surgery and also mortality, but the differences were statistically significant in only one study [45] regarding the morbidity of the disease. The main criticism of this study is the number of patients enrolled and the low dosage of gabexate (up to 900 mg/day) and the suggestion of the Authors was to start further studies involving a larger number of patients and using a higher dosage of the drugs.

In the 90s three main studies, from Germany, Italy and China, were published [47, 48, 49]. All trials were controlled, with a sufficient number of patients in two studies and with a high dosage of gabexate (from 2.4 to 4 g/day). The negative results of the German study [47], lacking effects of morbidity and mortality, contrast with the positive results from the other studies [48, 49] which demonstrated a significant reduction of the frequency of complications and the need for surgery in patients treated with gabexate. Early and late mortality were also decreased in a statistically significant manner in only one study [49]. Trying to explain the reason for these conflicting results may be apparently difficult, but we would stress how, in the German study, many biases might invalidate the results obtained, such as the age of the patients (significantly higher in the gabexate group), the etiology of the disease (48% due to alcohol seems to be very different from those observed in other countries), the time of enrolment of the patients (up to 7 days) and the evaluation of the results (at 90 days). All two meta-analyses published in the literature [50, 51], not including the Chinese study [49], confirm the statistically significant reduction of complications in patients suffering from acute pancreatitis and treated with gabexate vs. placebo. They also confirm the reduction of mortality in the gabexate group, but not in a statistically significant manner.

The results of the clinical study seem to indicate the therapeutic use of gabexate in the treatment of the severe form of acute pancreatitis [52], as recommended by Italian [53] and Japanese [54] guidelines. However, the best information these clinical studies give us is that, to work correctly, the gabexate treatment should be administered as early as possible and no later than 72 hours after onset and the dosage should be adequate.

Antiproteases and Prevention of Acute Pancreatitis

From the results of experimental and clinical studies on acute pancreatitis, an ideal model to demonstrate the effectiveness of gabexate is the prevention of acute pancreatitis secondary to endoscopic manipulation of the papilla of Vater. In this case we know the time of induction of pancreatitis, we may administer the drug before the induction of pancreatitis, at an appropriate dosage and for an adequate period of time. Recently, Di Francesco *et al*. demonstrated the inhibitory action of gabexate on sphincter of Oddi motility [55], already described in dogs [56], in patients with acute recurrent pancreatitis indicating a further potential mechanism able to reduce the incidence of acute pancreatitis in patients undergoing endoscopic procedures on the papilla of Vater.

From clinical studies, we know that in patients who develop acute pancreatitis, we may observe an increase of serum pancreatic enzymes after 2-4 hours [57, 58, 59, 60] and the onset of pain between the 3rd and the 7th hour after endoscopic maneuvers on the papilla [61, 62]. In patients who develop a severe post-ERCP acute pancreatitis, IL-6 will be elevated after 12-24 hour and the C-reactive protein will rise after the 48th hour [63, 64]. Therefore, we may postulate that the initial increase of serum amylases and/or lipase, observed in a large part of patients who undergo ERCP (up to 70%), is not a sign of acute pancreatitis, but is probably only a phenomenon secondary to a basolateral leakage of the enzymes from the acinar cells. The clinical onset of pain probably represents the real beginning of the disease, with the presence of oedema and/or necrosis in the pancreatic gland.

In Japan, gabexate has been used as a prophylaxis against serum pancreatic-enzyme

elevations [65, 66] and acute pancreatitis [67, 68] after endoscopic procedures, but the results are not conclusive due to the low number of patients enrolled.
In 1996, the first multicenter double-blind Italian study on the use of gabexate for the prevention of acute pancreatitis secondary to endoscopic maneuvers of the papilla of Vater was published [69]. In this study, involving a very large number of patients (208 in the treated group and 210 in the placebo group), the administration of 1 g of gabexate, from 30-90 min before up to 12 hours after ERCP, significantly reduced the number of cases of acute pancreatitis in the treated group vs. the placebo group (2% vs. 8%). The main drawbacks to this study are the high cost and the long period of administration of the drug. Hence, a second multicenter double-blind Italian study was designed to reduce the time of administration of the drugs. In this study, the Authors compared a 6.5 hour (500 mg) vs. a 13 hour infusion (1 g) of gabexate and clearly demonstrated a similar incidence of acute pancreatitis in the two treated groups (2.3% vs. 1.4%) [70]. We may conclude that the cost of the procedure is not so expensive as previously thought (41 USD per patient), suggesting it might be recommended for all patients requiring ERCP, but, more importantly, that the 6.5 hour infusion of gabexate is a sufficient time to prevent post-ERCP acute pancreatitis.
However, if treatment with gabexate is stopped two hours after the ERCP, as in the latest study appearing in the literature [71], the effect of the drug seems to be lost and gabexate does not prevent the onset of acute pancreatitis, suggesting that a 2-hour infusion is a too short an interval of time to interfere with the onset of post-endoscopic pancreatitis.

Conclusions

All experimental and clinical studies (prevention and treatment of acute pancreatitis) indicate the value of using gabexate in the prophylaxis of post-ERCP acute pancreatitis.

The cost of the procedure seems to be inexpensive (41 USD) and the amount of time necessary (6 hours) is also acceptable for out-patients who undergo ERCP. The lower cost of the short term infusion of gabexate raises the cost-benefit ratio in the treatment of all patients in need of ERCP, considering that two cost-effectiveness studies involving a 12 hour administration of gabexate to every patient undergoing ERCP showed the acceptable cost-benefit ratio of this approach [72, 73].

Key words Acute Disease; Chemicals and Drugs Category; Cytokines; Gabexate; Pancreatitis; Primary Prevention; Protease Inhibitors; Serine Proteinase Inhibitors

Abbreviations CDE: coline deficient ethionin; *ctsb*: cathepsin B; ELAM-1: endothelial leucocyte adhesion molecule-1; ICAM-1: intercellular adhesion molecule-1; MOF: multi-organ failure; SIRS: systemic inflammatory response syndrome

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