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ROUND TABLE

Antiproteases in Preventing Post-ERCP Acute Pancreatitis

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Summary

Pancreatitis remains the most common and potentially fatal complication following ERCP. Various pharmacological agents have been used in an attempt to prevent post-ERCP pancreatitis, but most randomized controlled trials have failed to demonstrate their efficacy. Antiproteases, which have been clinically used to manage acute pancreatitis, would theoretically reduce pancreatic injury after ERCP because activation of proteolytic enzymes is considered to play an important role in the pathogenesis of post-ERCP pancreatitis. Gabexate and ulinastatin have recently been evaluated regarding their efficacy in preventing post-ERCP pancreatitis. Long-term (12 hours) infusion of gabexate significantly decreased the incidence of post-ERCP pancreatitis; however, no prophylactic effect was observed for short-term infusion (2.5 and 6.5 hours). These results may be due to the short-life of gabexate (55 seconds). Since long-term infusion requires additional hospitalization, the use of gabexate in all patients at average risk of developing post-ERCP pancreatitis is an expensive strategy. Ulinastatin has a half-life of 35 minutes and can be given as a bolus infusion. Short-term (10 minutes) administration of ulinastatin showed a significant reduction in the incidence of post-ERCP pancreatitis in one randomized controlled trial. Ulinastatin is superior to gabexate in terms of cost because it does not require additional hospitalization. At present, there is no other randomized, placebo-controlled trial on ulinastatin under way.
Large scale randomized controlled trials revealed that both the long-term infusion of gabexate and the short-term administration of ulinastatin may reduce pancreatic injury, but these studies involve patients at average risk of developing post-ERCP pancreatitis. Additional research is needed to confirm the preventive efficacy of these antiproteases in patients at a high risk of developing post-ERCP pancreatitis.

Introduction

ERCP is widely performed for the diagnosis and management of various pancreaticobiliary diseases. Early complications after ERCP include acute pancreatitis, bleeding, perforation, and infection (cholangitis and cholecystitis) [1, 2]. Of these ERCP-related complications, pancreatitis remains the most common, with a reported incidence of 2 to 15% in multicenter prospective studies [3, 4, 5]. Most cases of post-ERCP pancreatitis are mild, showing complete recovery in a few days. After severe ERCP-related pancreatitis, however, secondary consequences (e.g. pancreatic pseudocyst and abscess) and multiorgan failure frequently develop; surgical intervention and prolonged hospital stay are usually required, and eventually the patient dies. In a reported series of 7,869 patients undergoing diagnostic or therapeutic ERCP, 3 patients (0.04%) died from severe

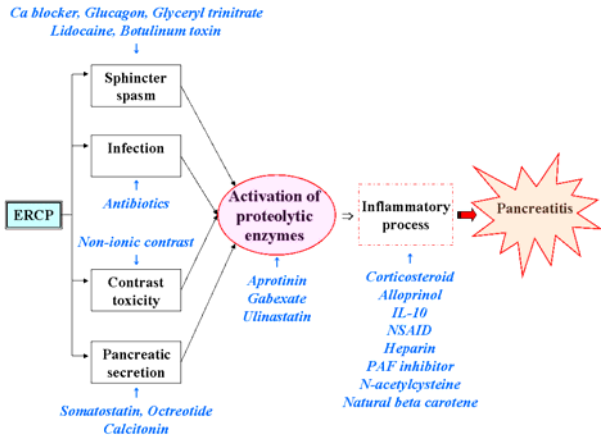

Figure 1. Postulated pathogenesis of the development of post-ERCP pancreatitis and potential pharmacological prevention.

post-ERCP pancreatitis [3, 4, 5]. The prevention of post-ERCP pancreatitis has been a never-ending challenge ever since ERCP was introduced in clinical settings in the 1970s.

The exact pathogenesis of post-ERCP pancreatitis has remained unclear but diverse factors, which include mechanical injury, hydrostatic injury, chemical and allergic injury, enzymatic injury, infection and thermal injury, have been postulated as causes of post-ERCP pancreatitis [6, 7, 8]. Many pharmacologic agents of different types have been used to prevent post-ERCP pancreatitis on the assumption that they pharmacological-ly inhibit one or more of the aforementioned factors associated with pancreatic damage (Figure 1). Irrespective of the etiology of acute pancreatitis, the activation of proteolytic enzymes, starting with trypsinogen activation to trypsin in pancreatic acinar cells, has been considered to play an initial role in the pathogenesis of pancreatitis. Trypsin would subsequently trigger the activation of other enzymes and the inflammatory cascade. On the basis of this pathogenesis, antiproteases, which have been used to manage acute pancreatitis in routine clinical settings in some countries, may be theoretically useful for preventing pancreatitis after ERCP. Since we know the timing for the development of pancreatitis after ERCP, adequate doses of antiproteases could be administered prophylactically. Currently, three anti-proteases, aprotinin, gabexate, and ulinastatin, have been evaluated for their prophylactic efficacy against post-ERCP pancreatitis in prospective randomized controlled trials (RCTs) (published in peer-review English journals) [9, 10, 11, 12, 13]. Since aprotinin was found to be ineffective in 1977 [9] and no further RCTs of aprotinin have been conducted, this review will focus on the efficacy of gabexate and ulinastatin regarding the prevention of post-ERCP pancreatitis.

Efficacy of Gabexate Regarding the Prevention of Post-ERCP Pancreatitis

Gabexate has had a long history regarding the prevention of pancreatic injury after ERCP. In the late 1970's, Japanese investigators had already evaluated the efficacy and safety of gabexate in this regard [14, 15]. While the results of these studies were encouraging, the number of patients enrolled was limited and study designs appeared to be inadequate. Nevertheless, these studies showed that prophylactic administration of gabexate was safe.

In 1996, Cavallini *et al*. reported the results of a well-designed multicenter RCT of gabexate for preventing post-ERCP pancreatitis [10]. They administered 1g of gabexate or a placebo intravenously from 30-90 minutes before ERCP and for 12 hours afterwards. Although no significant difference was seen in the incidence of hyperenzymemia between the 2 groups, the rate of post-ERCP pancreatitis was significantly lower in the gabexate group than in the placebo group (5/208, 2.4% *vs*. 16/210, 7.6%; P=0.003). In addition, all 5 patients with pancreatitis in the gabexate group were graded as mild whereas one-third of the patients in the placebo group developed necrotizing pancreatitis. At that time, gabexate was the first drug to have shown a preventive effect against post-ERCP pancreatitis in a multicenter RCT; the results were impressive, but some drawbacks of gabexate in this study were pointed out [16]. The main drawback was its long-term administration. The continuous 12-hour infusion regimen is inconvenient and requires an overnight hospital stay after ERCP. Since

diagnostic ERCPs as well as therapeutic procedures are routinely performed on an outpatient basis in the United States [17, 18] and some other countries [19, 20], the cost of this regimen was expensive.

Responding to these criticisms, the same authors conducted another RCT comparing a 6.5-hour infusion of 0.5 g gabexate to a 13-hour infusion of 1 g gabexate and found that the frequency of post-ERCP pancreatitis was similar between the 2 regimens [21]. They concluded that the preventive effect of the short-time (6.5 hours) infusion was equivalent to the long-term (13 hours) one. Unfortunately, there was no placebo group in this comparative study presumably for ethical reasons and, therefore, their conclusion was not convincing. In addition, a year after this report, Andriulli *et al*. found, in a large scale multicenter randomized placebo-controlled trial, that the 6.5-hour infusion of 0.5 g gabexate did not prevent post-ERCP pancreatitis [12]. The same authors also reported three meta-analyses of the prophylactic effect of gabexate on post-ERCP pancreatitis in 2000 [22], 2002 [11] and 2007 [23]. The first and second meta-analyses showed that gabexate significantly reduced the incidence of pancreatitis, but the preventive effect was lost when gabexate was given for a short-term (less than 4 hours) [11, 22]. Furthermore, the third meta-analysis reported in 2007 suggested that gabexate was ineffective even when administered as a long-term infusion (greater than 12 hours) [23]. Although, in general, a meta-analysis compensates for the disadvantages of a single RCT and provides solid evidence, it appears to be difficult to draw conclusions from their latest meta-analysis because this study added only one negative RCT of long-term infusion of gabexate, which was published in an abstract form only [24]. At present, we consider that a short-term (less than 6.5 hours) infusion of low-dose (less than 0.5 g) gabexate, which has been employed empirically in many institutions in Japan, has no protective effect on post-ERCP pancreatitis and an adequate dose (greater than 1 g) of gabexate should be administered continuously for a long period of time (greater than 12 hours)in order to prevent pancreatitis.

Efficacy of Ulinastatin Regarding the Prevention of Post-ERCP Pancreatitis

Ulinastatin is an intrinsic trypsin inhibitor extracted and purified from human urine which inhibits various enzymes such as alpha-chymotrypsin, lipase, amylase, elastase, and carboxylase. Ulinastatin has been used clinically to treat acute pancreatitis, mainly in Japan and China [25, 26, 27]. Furthermore, this agent has been given routinely in many Japanese institutions as a prophylactic to prevent post-ERCP pancreatitis. The main advantages of ulinastatin over gabexate are as follows: a) the inhibitory effect of ulinastatin on pancreatic enzymes is stronger than that of gabexate [28, 29, 30]; b) in various experimental models of pancreatitis, suppression of the development and progression of pancreatitis is more potent in the ulinastatin group than in the gabexate group [28, 29]; and c), since its serum half-life is relatively long (35 minutes), ulinastatin can be administered by bolus injection [31] in contrast to gabexate.

Ulinastatin would be superior to gabexate with regard to clinical use if a short-term administration of ulinastatin reduced the incidence and severity of pancreatitis after ERCP. In 1990, a Japanese non-randomized study revealed that a bolus injection of ulinastatin prevented pancreatic damage after ERCP more effectively than continuous injection [32]. Consequently, we conducted the first multicenter randomized placebo-controlled trial on ulinastatin for the prevention of post-ERCP pancreatitis [13]. A series of 406 patients, who underwent diagnostic or therapeutic ERCP for the first time, was finally evaluated. Ulinastatin 150,000 U dissolved in 100 mL of 0.9% saline solution or a placebo (100 mL of 0.9% saline solution) were administered intravenously immediately before ERCP for 10 minutes. The incidence of hyperenzymemia was significantly lower in the ulinastatin group than in the placebo group (amylase, P=0.011; lipase, P=0.008). In

addition, ulinastatin significantly reduced the rate of post-ERCP pancreatitis (6/204, 2.9% *vs*. 15/202, 7.4%; P=0.041). The severity of the pancreatitis, which was defined according to the 1991 Consensus Guidelines [1], was not significantly different between the 2 groups. Using multivariate analysis, we found that therapeutic ERCP and the absence of ulinastatin administration were significant risk factors for the occurrence of post-ERCP pancreatitis. Currently, no other randomized placebo-controlled trials on ulinastatin for post-ERCP pancreatitis are available.

Which is the Ideal Prophylactic Drug for Post-ERCP Pancreatitis: Gabexate or Ulinastatin?

A number of pharmacologic agents have been evaluated for their prophylactic efficacy against post-ERCP pancreatitis [10, 11, 12, 13, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46] (Table 1). However, attempts to prevent pancreatitis have, for the most part, been disappointing. Although some drugs (e.g. IL-10 [34], antibiotics [35], diclofenac [38], and somatostatin [39]) may potentially decrease pancreatic damage, as shown by single center RCTs, large multicenter RCTs are mandatory in order to substantiate convincing results. At present, gabexate and ulinastatin are the pharmacologic agents which have been shown to be effective in preventing pancreatitis in a multicenter randomized placebo-controlled trial [10, 13].

Two Japanese RCTs comparing gabexate with ulinastatin suggested that the preventive effect of gabexate was equivalent to that of ulinastatin [47, 48]. However, no definite conclusions can be drawn from these two studies mainly due to the limited number of patients enrolled and their inadequate study design. Similarly, it may be of little value to compare the efficacy of these two protease inhibitors in preventing post-ERCP pancreatitis from the results of different RCTs because the patient population, the endoscopists' expertise, endoscopic procedures performed and the definition of post-ERCP pancreatitis, which could all influence the incidence of pancreatitis, differ greatly. Nevertheless, it is interesting to note that the frequency of post-ERCP pancreatitis in the placebo group is similar across large-scale multicenter placebo-controlled trials of gabexate or ulinastatin [10, 11, 13] except for the RCT by Andriulli *et al*. published in 2004 [12] (Figure 2).

The ideal drug for preventing post-ERCP pancreatitis should meet the following three conditions: a) the safety of the drug should be guaranteed; b) prolonged administration and additional hospital stay should not be

Table 1. Pharmacological prevention of post-ERCP pancreatitis: randomized controlled trials (1996-2006).

Drug, year	Total number of patients	Efficacy	Multicenter RCT
Gabexate (1g, 12 h), 1996 [10]	**418**	**Yes**	**Yes**
Gabexate (0.5 g, 6.5 h), 2004 [12]	1,127	No	Yes
Octreotide, 2001 [33]	114	No	Yes
IL-10, 2001 [34]	137	Yes	No
Antibiotics, 2001 [35]	315	Yes	No
Nifedipine, 2002 [36]	155	No	No
Corticosteroid, 2003 [37]	1,115	No	Yes
Dicrofecac, 2003 [38]	220	Yes	No
Somatostatin (250 μg, bolus), 2003 [39]	270	Yes	No
Somatostatin (750 μg, 6.5 h), 2004 [12]	1,127	No	Yes
Heparin, 2004 [40]	448	No	Yes
Natural beta-carotene, 2004 [41]	321	No	No
Botulinum toxin, 2004 [42]	26	No	No
Lidocaine, 2004 [43]	294	No	No
Alloprinol, 2005 [44]	701	No	Yes
Ulinastatin, 2005 [15]	**406**	**Yes**	**Yes**
N-acetylcysteine, 2006 [45]	249	No	No
Glyceryl trinitrate, 2006 [46]	318	No	No

required; and c), the drug should be effective even in patients at high risk for post-ERCP pancreatitis.

a) Safety of Antiproteases to Prevent Post-ERCP Pancreatitis

The safety of the drug is the most important condition to be fulfilled because it is given as a prophylactic. In contrast to aprotinin (a classic protease inhibitor), gabexate (a synthetic protease inhibitor) is not antigenic and, hence, has been regarded as safe. Of the 1,220 patients who received gabexate to prevent post-ERCP pancreatitis, none of them developed severe gabexate-related adverse events irrespective of the dose and infusion time [10, 11, 12, 21].

Ulinastatin, an endogenous trypsin inhibitor, has also been considered to be safe. In our study, none of the 204 patients in the ulinastatin group developed adverse events related to short-term ulinastatin (150,000 U) administration for (10 minutes) [13]. Additionally, no serious side effects of ulinastatin have been observed in the series reported [32, 47, 48]. Therefore, we would like to conclude that these antiproteases are very safe when administered as a prophylactic.

The effect of the drug on the sphincter of Oddi function is a matter of considerable concern. The divergent results between two antisecretory agents, secretin and octreotide, have been postulated to be attributable to their effects on the sphincter function [11, 12]; somatostatin reduces the contractility of the sphincter of Oddi [49] while octreotide raises the sphincter pressure [50, 51]. Gabexate has been demonstrated to reduce the sphincter of Oddi pressure [52, 53], suggesting a theoretically beneficial effect which would mitigate pancreatic damage after ERCP. On the other hand, the pharmacological effects of ulinastatin on the sphincter of Oddi have not yet been evaluated. In our study, however, no significant difference was seen between the ulinastatin and the placebo group with regard to the difficulty of cannulation [13]. It appears that ulinastatin has no adverse effects on the sphincter of Oddi.

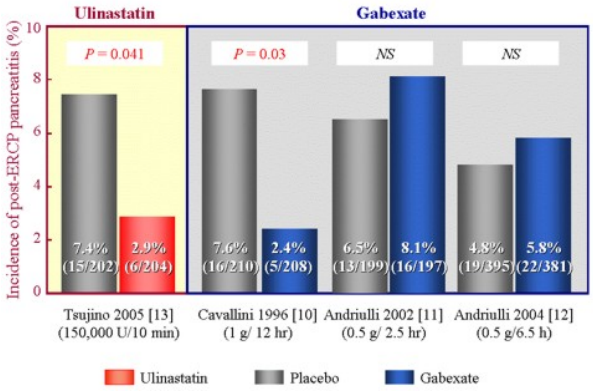

Figure 2. Results of randomized controlled trials of gabexate and ulinastatin regarding prevention of post-ERCP pancreatitis.

b) Efficacy of Antiproteases Administered by a Short-Term Infusion

The first large RCT on gabexate by Cavallini *et al*. demonstrated that gabexate was effective in preventing post-ERCP pancreatitis when given by long-term infusion (12 hours) [10]. However, subsequent RCTs by Andriulli *et al*. revealed that the preventive effect of gabexate was lost when administered for both 2.5 hours [11] and 6.5 hours [12]. The same authors also found, using meta-analysis that short-term (less than 4 hours) infusion of gabexate did not prevent pancreatitis [11]. The discrepancy over the protective effects of short-term and long-term infusion of gabexate is probably ascribable to its short half-life (55 seconds).

We have clearly demonstrated that a short-term (10 minutes) infusion of ulinastatin significantly reduced the frequency of pancreatitis [13]. This favorable result may be related to its relatively long half-life (35 minutes) [31]. In addition, an adequate serum concentration of ulinastatin is reached immediately after short-term infusion [31]. Recent investigations on post-ERCP pancreatitis have shown that, in patients who develop post-ERCP pancreatitis, the onset of pancreatic damage may occur during or immediately after the procedure [54, 55, 56]. Messmann *et al*. showed that serum lipase levels were increased one hour after the procedure in patients with post-ERCP pancreatitis [54]. Therefore, short-term infusion of ulinastatin seems reasonable for

maximizing the inhibitory effect of ulinastatin on the initial event of pancreatic damage. In a non-randomized trial comparing bolus injection *vs*. continuous infusion of ulinastatin, serum amylase levels were significantly lower at 5 hours after ERCP in the bolus injection group [32].

The strategy adopted in our RCT may be beneficial with regard to costs because short-term infusion of ulinastatin before ERCP does not require additional hospitalization in contrast to long-term infusion of gabexate. Furthermore, the cost of 150,000U of ulinastatin is lower than that of 1g of gabexate (41 US$ *vs*. 82 US$). Although Cavallini *et al*. claimed that a 12-hour administration of gabexate reduced the costs as compared to a placebo [57], a 10-minute infusion of ulinastatin might be an even less expensive strategy.

c) Efficacy of Antiproteases in Patients at a High Risk of Developing Post-ERCP Pancreatitis

Recent multicenter prospective studies have identified patients who are at a high risk of developing post-ERCP pancreatitis, the very group of patients in whom the incidence and severity of pancreatitis should be reduced [2, 3, 4, 5]. The first RCT of gabexate which demonstrated its efficacy in preventing post-ERCP pancreatitis involved unselected patients with average risks for pancreatitis [10]. As the authors did not provide stratified data on high risk patients, it was unclear whether long-term infusion of gabexate would have prevented pancreatitis in the subgroup of high risk patients. A subsequent RCT by Andriulli *et al*. demonstrated no significant benefit of a 2.5 hour infusion of gabexate in high risk patients (8.1% in the gabexate group *vs*. 6.5% in the placebo group) [11].

Our RCT on ulinastatin also included average risk patients; post-ERCP pancreatitis occurred in 7.4% of the patients in the placebo group [13]. However, in the same study, we evaluated the efficacy of ulinastatin, using multivariate analysis, in patients who underwent therapeutic ERCP, i.e., the subgroup of patients who were at a significant risk of developing post-ERCP pancreatitis. No statistically significant difference in the frequency of pancreatitis was observed between the ulinastatin group and the placebo group, but ulinastatin tended to be more beneficial (5/118, 4.2% *vs*. 12/109, 11.0%; P=0.053). We also found that ulinastatin significantly reduced the incidence of pancreatitis in patients subjected to pancreatography. Pancreatic duct injection has been identified as a definite risk factor for post-ERCP pancreatitis [2, 4, 5]. Because the primary endpoint of our study was the efficacy of ulinastatin in patients with average risks for pancreatitis, it appears inadequate to draw a conclusion regarding the preventive effect of ulinastatin in patients at high risk for post-ERCP pancreatitis.

Conclusions

From the results of a well-designed multicenter RCT, gabexate may be beneficial in preventing post-ERCP pancreatitis in average risk patients when administered for a long period while a complete paper on a negative RCT, which makes use of a similar strategy and which is currently available only in abstract form, is awaited. Short-term infusion of ulinastatin is also effective in reducing the incidence of pancreatitis and is likely to be more cost-effective than long-term infusion of gabexate. To ensure convincing results, additional well-designed multicenter RCTs of ulinastatin are needed.

We completely agree with the suggestion of Freeman [8] and Testoni [58] that the best way to prevent post-ERCP pancreatitis is to avoid the performance of unnecessary ERCPs in high risk patients. However, there may be a subgroup of patients who could benefit from therapeutic ERCP despite the high risk of developing pancreatitis. Further studies are necessary to determine the efficacy of gabexate and ulinastatin in this group of patients.

Keywords Gabexate; Pancreatitis, Acute Necrotizing; urinastatin

Abbreviations RCT: randomized controlled trial

Conflict of interest The authors have no potential conflicts of interest

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