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Preventing Post-ERCP Pancreatitis: Where Are We?

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Summary

Acute pancreatitis still represents the most common complication after procedures involving Vater's papilla; the reported incidence of this complication varies from less than 1% up to 40%. Attempts at preventing post-ERCP pancreatitis have been carried out using technical measures, pharmacological prophylaxis, or patient selection. Balloon sphincter of Oddi dilatation, difficult papillary cannulation, pancreatic sphincterotomy and multiple pancreatic duct injections have been found to be risk factors for postprocedure pancreatitis. Therefore, technique-related prevention of post-ERCP pancreatitis includes careful pancreatic duct injection, avoiding cannulation trauma, and maintaining adequate pancreatic drainage after the ERCP procedure. Pancreatic stent placement has been shown to be the most effective technique-related prevention of postprocedure pancreatitis. Apart from technique-related risk factors, operator experience also seems to be a potential risk-factor for post-ERCP/ES complications. The experience of the endoscopist rather than other patient- or technique-related conditions could probably constitute the major risk factor for postprocedure pancreatitis.

Pharmacological prevention of pancreatitis after ERCP or sphincterotomy has been the topic of several investigations in recent years but still remains a debated question. Pharmacological prevention has been mainly aimed at either reducing the amount of intrapancreatic enzymes, preventing intracellular co-localization of enzymes and lysosomal hydrolases or blocking some steps of the enzyme-activated inflammatory cascade. Somatostatin, octreotide, gabexate mesilate and, more recently, recombinant interleukin-10 have been the most investigated drugs. Somatostatin, gabexate mesilate and recombinant interleukin-10, but not octreotide, have been found to be able to prevent post-ERCP pancreatitis in non-selected cases; however, a strategy of routine pharmacological prophylaxis in all patients is not likely to be cost-effective. A strategy of pharmacological prevention only in high-risk cases is cost-effective, but, up to now, only recombinant interleukin-10 has been proven effective. The "on demand" postprocedure treatment should also be of paramount importance, but no data are at present available regarding the potential efficacy of some drugs; on the basis of the mechanism of action, we can argue that recombinant interleukin-10 could be the only drug candidate for such a strategy.

Post-ERCP pancreatitis can also be prevented by patient selection. Patient-related risk factors are now well-known, so an increased risk of developing pancreatitis is predictable "*a priori*" in these subjects, independently of the type of endoscopic procedure performed. Furthermore, the risk of pancreatitis escalates when multiple risk factors occur in the same patient or some technique-related risk factor comes up during the procedure. In these patients diagnostic ERCP should be avoided in routine practice and magnetic resonance

cholangio-pancreatography should be used as the first diagnostic step. When either diagnostic or therapeutic ERCP is indicated, these high-risk patients should be informed about their own specific risk of postprocedure pancreatitis.

Introduction

Acute pancreatitis still represents the most common complication after procedures involving Vater's papilla; the reported incidence of this complication varies from less than 1% up to 40%, but rates of about 5% are reported in most prospective studies involving non-selected patients [1]. Different criteria for defining pancreatitis and methods of data collection, together with differences in patient populations (i.e. rate of high-risk patients included in the published series) are factors that are likely to affect the varying rate of postprocedure pancreatitis. Although most episodes of post-ERCP pancreatitis are mild (about 90%), a small percentage of patients (about 10%) may develop severe pancreatitis resulting in prolonged hospitalization, intensive unit care and utilization of major hospital resources; these patients also have a significant morbidity and mortality. Despite technical improvements in recent years and the increased experience of endoscopists in the use of ERCP procedures, the incidence of postprocedure pancreatitis has not yet decreased. Considering the above data, in the last decade, many efforts have been addressed to preventing this complication, most of them with disappointing results.

Attempts at preventing post-ERCP pancreatitis have been made using technical measures or pharmacological prophylaxis and patient selection has also been seen to be of paramount importance.

Technique-Related Prevention

Balloon sphincter of Oddi dilatation, difficult papillary cannulation, pancreatic sphincterotomy and multiple pancreatic duct injections have been found to be independent risk factors for postprocedure pancreatitis (Odds ratio of 4.5, 3.4, 3.1, 2.7, respectively) in the recent prospective, multicenter study by Freeman *et al.* [2].

Cannulation trauma to the papilla is the most common cause of sphincter of Oddi spasm and/or papillary oedema, thus creating an obstacle to the flow of pancreatic juice with subsequent acute pancreatic inflammation. The importance of this mechanism in the development of acute pancreatitis has been recently highlighted by a Japanese group [3]: in their study, the authors showed that, although the frequency of endoscopic sphincterotomy (ES)-induced pancreatitis is significantly higher than that of post-ERCP pancreatitis, the frequency of severe pancreatitis within 48 hours and the worsening of pancreatitis after 48 hours is significantly lower within the group of patients who contracted ES-induced pancreatitis; thus, the lowering of intraductal pressure after ES mitigates the severity of post-procedural pancreatitis. In fact, pancreatic stent placement has been shown to be the most effective technique-related prevention of postprocedure pancreatitis; placement of a 3-5 F stent into the pancreatic duct has been shown to significantly reduce the risk of pancreatitis after biliary sphincterotomy for sphincter of Oddi dysfunction [4, 5], pancreatic sphincterotomy [6], balloon-dilation of the biliary sphincter for biliary stone removal [7], and prior to precut sphincterotomy [8]. However, pancreatic stenting on a regular basis may be difficult to perform and generally it tends to be done relatively late in the procedure, mainly when difficult cannulation occurs, probably after the damage has already been done; moreover, repeated unsuccessful attempts by endoscopists who are unfamiliar with this procedure may leave the patient worse off than if no attempt had been made. Pancreatic duct stenting only "on demand" for high risk procedure-related conditions and not by routine gave equivocal benefit, as documented in a randomized trial [9]; severe pancreatitis however did not occur in the group receiving pancreatic stents. Placement

of small caliber stents early in the procedure in all high risk patients and for difficult cannulation in patients who are younger, female and who have a normal pancreas should therefore be recommended as the most effective available tool in preventing postprocedure pancreatitis or at least in reducing its severity.

Opacification of the main pancreatic duct alone is associated with a 31% incidence of hyperamylasemia; this figure is similar to the 24% incidence of hyperamylasemia which occurs after cholangiography alone [9]. This suggests that mechanical entry into the duct is a less important cause of hyperamylasemia than other potential factors. However, multiple pancreatic duct injections significantly increase the risk of post-ERCP pancreatitis; therefore, the endoscopist must balance the need for specific duct visualization against the possible provocation of complications. Guide-wire cannulation may be used to avoid repeated, undue opacification of the pancreatic ductal system. Although the use of disposable sets including sphincterotomes supplied with guide-wires has become routine practice in many centers, however, whether such an approach could effectively prevent pancreatic reaction still remains unknown, since no prospective, controlled studies are up to now available. At present, only one study regarding the experience of a routine guide-wire cannulation in a non-controlled series of consecutive patients has been presented as a poster and has shown encouraging results [10].

Injection pressure and volume of the contrast medium injected into the pancreatic duct both contribute to ductal epithelial or acinar injury. This injury probably occurs from the disruption of cellular membranes or tight junctions between the cells with a backflow of the intraductal content into the interstitial space [11]. Elevation of the pancreatic enzyme level has been shown to depend on the volume of the contrast medium injected [12]. Acinarization occurs when the volume injected into the pancreatic duct exceeds the ductal capacity; it may also occur in the presence of a rapid rate and high-pressure injection [13, 14]. Reducing the injection pressure can therefore minimize the risk of either pancreatic ductal lesions or acinarization. Although several studies have demonstrated a correlation between the elevation of serum pancreatic enzyme levels and the degree of duct opacification [9, 13, 14, 15, 16, 17], acinarization "*per se*" seems to be less important than generally thought [2, 18, 19, 20]. In the study of Freeman *et al.* [18], even if the acinarization of the pancreas was significantly more frequent in patients who developed pancreatitis at univariate analysis, this risk disappeared at multivariate analysis when ES was performed.

The osmolarity and ionic nature of the contrast media are believed to play some role in the occurrence of post-ERCP pancreatitis, so that investigators have used low-osmolarity agents, usually non-ionic, to reduce the rate of this complication. Results of previous studies comparing different contrast media have been inconclusive [17, 21, 22, 23 24]; however, non-ionic, low-osmolarity contrast media should be preferred in clinical practice.

Deep, blind cannulation increases the chances of submucosal papillary lesions or pancreatic duct perforation with associated submucosal or intraparenchymal contrast injection; submucosal injection renders further endoscopic maneuvers difficult, while duct perforation more commonly causes acute pancreatic inflammation [25]. Long-nose cannulotomes should therefore be used with caution for specific purposes and not in routine practice for standard cannulation.

Balloon-dilation of the biliary sphincter has been introduced as an alternative to sphincterotomy for the extraction of bile duct stones [26, 27]. It is not clear whether or not this procedure is associated with a major risk of postprocedure pancreatitis, since the published studies available report conflicting data [2, 28, 29, 30]. Based on the results of their study, Freeman *et al.* concluded that balloon dilation for extraction of bile duct stones should not be recommended as a

standard approach, especially in high risk subjects, unless there is a contraindication to sphincterotomy.

Electrocautery in the vicinity of the pancreatic duct orifice may produce oedema of the tissue surrounding the orifice with subsequent obstruction of the outflow of pancreatic juice. Bipolar cautery was shown in one study to result in significantly lower rates of pancreatitis than conventional monopolar cautery (0% vs. 6%) [31]. A more recent study has shown that pure cutting current significantly reduced pancreatitis rates when compared with the more conventional blended current (3% vs. 11%) [32]. Automatic current delivery systems are increasingly used but it is still unclear whether or not they can modify the rate of postprocedure pancreatitis; preliminary data suggest no difference in pancreatitis rates as compared to conventional blended current [33].

Precut, or access papillotomy in order to gain access to the common bile duct, has been associated with a higher risk of pancreatitis in multicenter studies involving endoscopists with varied experience [2, 18, 19, 20]; however, the complication rate does not seem different than for standard sphincterotomy when the precut is performed by experienced endoscopists [34, 35, 36, 37, 38, 39, 40], suggesting that the risk of complication is operator- and high risk conditions-dependent rather than technique-dependent. Use of pancreatic stents prior to needle-knife precut may significantly prevent the risk of postprocedure pancreatitis. [41].

Independently of the technique-related risk factors, operator experience also seems to be a potential risk-factor for post-ERCP/ES complications, although few studies have addressed the question. In one of the two largest Italian multicenter prospective studies [19], the comparison of low- (less than 200 ERCPs/year) and large- (more than 200 ERCPs/year) volume centers showed significant differences in the outcome of ERCP. Large-volume centers had significantly less overall complications (2.0 % vs. 7.1 %, $P<0.001$) and less complication-related deaths (0.18 % vs. 0.75 %, $P<0.05$), while the risk of pancreatitis was significantly increased in low-volume centers in the univariate analysis (relative risk 2.8). In a retrospective study regarding the impact of skill and experience of the endoscopist on the outcome of endoscopic sphincterotomy techniques, Rabenstein *et al.* [42] found that cumulative live-time volumes of the endoscopists ("ERCP-experience") had no influence on the occurrence of complications, while a low ERCP-frequency (ongoing volumes less than 40 procedures per year) was the only significant risk factor for complications (9.3 % vs. 5.6 %; $P<0.05$). These data were further confirmed in a prospective study [43]; therefore, the Authors suggested that the experience of the endoscopist rather than other patient- or technique-related conditions could probably constitute the major risk factor for postprocedure pancreatitis.

Pharmacological Prevention

Pharmacological prevention of pancreatitis after ERCP or sphincterotomy has been the topic of several investigations in recent years but still remains a debated question. In the last three years, 14 papers have been published with conflicting results, investigating the prophylactic efficacy of octreotide, steroids (three papers, respectively), somatostatin, interleukin-10 (two papers, respectively), gabexate mesilate, heparin, allopurinol, nifedipine and antibiotics (one paper, respectively). The ideal pharmacological prophylaxis should be effective in patients who really risk developing postprocedure pancreatitis; it should be as cheap as possible and should not require prolonged administration in the post-procedure period.

The knowledge of the mechanisms involved in the early phase of onset of acute pancreatitis plays a pivotal role in the search for pharmacological prophylaxis of this complication. In experimental models of acute pancreatitis, it has been suggested that digestive enzyme activation might occur within acinar cells and it has been shown that in the early stages of acute pancreatitis there

is a co-localization of digestive enzymes and lysosomal hydrolases within large cytoplasm vacuoles. This co-localization mechanism might result in activation of the digestive enzymes, mainly trypsin. Cell injury induced by pre-mature intra-acinar trypsinogen activation to trypsin leads to oxidative stress, subsequent production of chemo- and pro-inflammatory cytokines, and contact system activation. This system has important inflammatory activity through release of the vasoactive peptide bradykinin. All these events take place within a very short period of time and a delay of only a few hours exists between the pancreatic injury induced by ERCP and the onset of pancreatitis. Drugs must therefore be able to prevent the trypsinogen activation to trypsin or modulate the severity of pancreatitis within a short "therapeutic window". Pharmacological prevention has therefore been mainly addressed to reducing the amount of intrapancreatic enzymes, preventing co-localization of enzymes and lysosomal hydrolases or blocking some steps of the enzyme-activated inflammatory cascade.

Somatostatin, octreotide, gabexate mesilate and, more recently, recombinant interleukin-10 have been the most investigated drugs.

Inhibition of exocrine pancreatic secretion can be obtained by somatostatin and its syntethic analogue, octreotide. The hormone and its analogue affect the exocrine function both directly, by reducing the secretion of digestive enzymes, and indirectly, by inhibiting secretin and cholecystokinin production. In addition to their antisecretory effects, somatostatin and octreotide have been demonstrated to modulate the cytokine cascade [44] and may also have a cytoprotective effect on pancreatic cells, although the mechanism whereby these agents exert their cytoprotective effect is unknown [45]. Octreotide has a longer biological half life. Experimental investigations have shown that both somatostatin and octreotide have a protective effect on experimental acute pancreatitis [46], thus the use of these drugs for the prevention of post-ERCP pancreatitis has a reasonable base.

Somatostastin has been administered for prophylactic purposes either by 2 to 26-hour prolonged i.v. infusion or by a single bolus administration immediately before the ERCP procedure. Between 1988 and 2002, thirteen randomized clinical trials were published on the prophylactic effect of somatostatin in preventing post-ERCP pancreatitis. A meta-analysis by Andriulli *et al.* [47] of all the clinical trials dealing with the use of prophylactic somatostatin to prevent post-ERCP pancreatitis which were published before the year 2000 indicated that somatostatin reduces the risk of post-ERCP pancreatitis with an odds ratio of 0.38 as compared to the control groups. However, the same Author recently reported in a randomized controlled multicenter trial on high-risk patients that the infusion of somatostatin at a dose of 750 μg started 30 minutes before the procedure and continued for two hours after did not reduce the incidence of post-ERCP pancreatitis as compared to the placebo group [48].

Octreotide has the advantage of a simple administration by subcutaneous injection; therefore, prophylactic treatment with octreotide is cheaper than with somatostatin. The simplest and cheapest prevention strategy, with a 100 μg subcutaneous bolus immediately before and one hour after ERCP and sphincterotomy, did not lower the incidence of post-ERCP hyperamylasemia or modify the risk of pancreatitis. This prophylactic approach aiming at inhibiting exocrine pancreatic secretion within the first hour after papillary manipulation did ensure a peak serum level of hormone at the time of papillary manipulation, and a subsequent subcutaneous dose was given to obtain a longer post-procedure effect. Subcutaneous injection of 0.2 mg of octreotide three times daily for three days effectively reduced both the incidence of post-ERCP hyperamylasemia and pain [49]; however, 24-hour prophylaxis using octreotide 30 minutes before the procedure did not reduce the incidence of pancreatitis in selected patients at high risk of post-ERCP pancreatitis [50]. From 1991 up to now, thirteen randomized clinical trials have

been published with mainly disappointing results, as reported in the meta-analysis of 10 clinical trials published before the year 2000 by Andriulli *et al.* [47] who concluded that octreotide was only associated with a reduced risk of post-ERCP hyperamylasemia but had no effect on acute pancreatitis and pain.

The overall evidence in the literature suggests that somatostatin is likely to be effective in reducing the frequency of post-ERCP pancreatitis, whereas octreotide is not. Whether the difference is related to the different effects of the two agents on the motor function of sphincter of Oddi or to other reasons is unclear.

Prevention of intra-acinar trypsinogen activation to trypsin and the subsequent inflammatory cascade may be achieved by using antiprotease agents. In 1995, we published a study [51] on the first attempt at a using C1-inhibitor (C1-INH) plasma concentrate. The blockage of ongoing complement and contact system activation by high doses of C1-INH has been reported to improve the outcome of acute pancreatitis in experimental models [52]. In 1996, gabexate mesilate was shown to be effective in preventing post-ERCP pancreatitis in a prospective, multicenter, controlled trial involving 276 patients [53]: the incidence of pancreatitis was reduced four-fold in the treatment group compared with the placebo group (2% vs. 8%). Other studies previously performed in Japan also documented beneficial effects [54, 55]. A disadvantage of the gabexate mesilate prophylaxis is the need for a 12-hour infusion; however, a recent multicenter study by the same group has demonstrated that a 6-hour infusion was as effective as a 12-hour infusion [56]. Overall, a meta-analysis study by Andriulli *et al.* evaluating six clinical trials published between 1978 and 1996 showed that gabexate mesilate was effective in preventing post-ERCP pancreatitis [47]. However, the same Author did not find any beneficial effect of the drug administered in high-risk patients over a two-hour period, starting 30 min before the procedure [48].

Based on their mechanisms of action, both anti-secretory and anti-protease agents may be beneficial only when administered before the procedure but do not seem to be able to prevent the inflammatory cascade, once activated, and, therefore, are likely to be ineffective if used "on demand" when technique-related high-risk conditions have occurred. Moreover, available data show that drugs are ineffective in high-risk subjects, the very subjects in whom there is a need for some pharmacological prophylaxis.

More recently, attempts to block the inflammatory cascade have been carried out by using an anti-inflammatory cytokine, the recombinant interleukin-10. Three of four randomized clinical trials have shown that prophylactic injection of interleukin-10 can significantly reduce the incidence of acute pancreatitis, and may decrease the length of hospital stay. In 2001, a single-center, double blind, placebo-controlled trial by Deviere *et al.* [57] compared a single injection of recombinant human interleukin-10 (at 2 different doses: 4 and 20 μg/kg respectively), given 30 minutes before the ERCP procedure, to a placebo; not only was the treatment able to significantly decrease the incidence of post-ERCP pancreatitis, but it was also proven effective in high risk cases. Another double-blind placebo-controlled study was published in 2001 but was not conclusive [58], probably because it focused on standard risk patients, including those undergoing diagnostic ERCP. Pooling all patients enrolled in the four available studies, the incidence of post-ERCP pancreatitis was 7.1% in the interleukin-10 groups and 13.9% in the placebo groups. A potential additional advantage of the use of recombinant interleukin-10 could be its efficacy even if administered "on demand" in the postprocedure period. Unfortunately, the high cost of this treatment constitutes a limiting factor for its routine administration in all patients.

A focal point in the pharmacological prevention of postprocedure pancreatitis is its cost-effectiveness: should the prophylaxis be

given to all patients undergoing ERCP procedure or only to those at high-risk? Since a number of conditions at high risk for developing postprocedure pancreatitis are not predictable before the procedure but come up during the procedure, a drug able to prevent pancreatic reaction even if administered after the procedure "on demand" would be welcome.

Although the mean incidence of post-procedure pancreatitis after diagnostic and therapeutic ERCP has been reported to be 5.2% and 4.1% respectively [1], in two recent, large, prospective Italian studies in non-selected patients, the incidence was 1.3% [19] and 1.9%, respectively [20]. The case-mix of the different series very likely influences the rates of post-procedure pancreatitis, which may depend more on the percentage of patients or procedures with some risk factors than on different definitions of pancreatitis, expertise or data collection methods. In fact, in the four prospective studies giving separate figures for standard- and high-risk patients, the reported incidence of pancreatitis was 1.6% and 7.8% [59], 3.4% and 29.2% [60], 3.6% and 19.1% [18], 0.4% and 18.8% [20], in patients with and without sphincter of Oddi dysfunction, respectively.

With an incidence of postprocedure pancreatitis lower than 5%, as reported in most non-selected patients, a routine prophylactic approach in all patients does not seem useful in most cases and is therefore costly; on the other hand, with an higher incidence of postprocedure pancreatitis, as reported in patients with risk factors (8-29%), a prophylactic approach may not only be justified, but would also be cost-effective. A theoretical analysis of cost-effectiveness and cost-benefit ratios of gabexate mesilate in post-ERCP pancreatitis [61] confirmed that, with an average 2% post-procedure pancreatitis rate as reported for non-selected patients in recent studies, and an estimated 50% efficacy of the drug, routine prophylaxis appears too expensive.

The meta-analysis by Andriulli *et al.* [47] showed that the number of non-selected cases needed to be treated to prevent one case of postprocedure pancreatitis was 13 for somatostatin and 27 for gabexate mesilate. These figures also indicate that a routine pharmacological prophylaxis in non-selected patients is unlikely to be cost-effective, since for every 100 patients undergoing ERCP under drug prophylaxis, the vast majority would receive the infusion needlessly. Gabexate mesilate strategy has been shown by Andriulli *et al.* to be more expensive than that of somatostatin. However, gabexate mesilate has been found effective in preventing postprocedure pancreatitis in non-selected cases also with a dosing regimen of a 6.5-hour infusion of 0.5 g of the drug [56]; halving the gabexate mesilate dosing regimen, together with an estimated actual cost in Italy of 87 euro per treatment, could also be economically advantageous for a routine prophylaxis with an average rate of pancreatitis of 5%.

Based on the above data, a strong argument can be made for pharmacological prophylaxis in high-risk groups, such as young patients and those with suspected sphincter of Oddi dysfunction, non-dilated biliary ducts or a history of pancreatitis. Few studies up to now have specifically addressed the question. Unfortunately, only interleukin-10 was proven effective in the study by Deviere *et al.* [57]; on the other hand, both somatostatin and gabexate mesilate were proven not to be effective by Andriulli *et al.* [48] but they used unusual regimen dosing in their study. Further studies are therefore needed.

In conclusion, somatostatin, gabexate mesilate and recombinant interleukin-10, but not octreotide, have been found to be able to prevent post-ERCP pancreatitis in non-selected cases; however, a strategy of routine pharmacological prophylaxis in all patients is likely not to be cost-effective. A strategy of pharmacological prevention only in high-risk cases is cost-effective, but, up to now, only recombinant interleukin-10 has been proven effective. "On demand" postprocedure treatment should also be of paramount importance, but no data are at present available on the potential efficacy of some drugs; on the basis of the mechanism of

action, we can argue that recombinant interleukin-10 could be the only drug candidate for such a strategy.

Patient Selection

Post-ERCP pancreatitis can also be prevented by patient selection. Patient-related risk factors are now well-known; therefore an increased risk of developing pancreatitis is predictable "*a priori*" in these subjects, independently of the type of endoscopic procedure performed; moreover, the risk of pancreatitis escalates when multiple risk factors occur in the same patient or technique-related risk factors come up during the procedure. For the same reasons, difficulty of cannulation, normal serum bilirubin, female gender, recurrent abdominal pain, absence of biliary obstruction, and conditions suggesting possible sphincter of Oddi dysfunction, all increase the risk of pancreatitis by more than 10-fold [2]. In these patients, diagnostic ERCP should be avoided in routine practice and magnetic resonance cholangio-pancreatography (MRCP) should be used as the first diagnostic step. When ERCP is indicated, either diagnostic or therapeutic, these high-risk patients should be informed about the specific risk of postprocedure pancreatitis.

Key words Acute Disease; Cholangiopancreatography, Cost-Benefit Analysis; Endoscopic Retrograde; Endoscopy; Pancreas; Pancreatitis, Acute Necrotizing; Preventive Medicine; Primary Prevention; Risk Factors; Sphincterotomy, Endoscopic

Abbreviations ES: endoscopic sphincterotomy; MRCP: magnetic resonance cholangio-pancreatography

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