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# Pharmacological Prevention of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis

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## Abstract

The incidence of clinically significant pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP) ranges from 1–13.5%. It is more common after therapeutic procedures such as sphincterotomy or balloon dilatation of the sphincter, and diagnostic procedures such as biliary or pancreatic manometry. The severity of post-ERCP pancreatitis may vary from very mild to extremely severe disease with multiple organ failure and fatal outcome. Several factors including papillary oedema, injection of hyperosmolar contrast-material, introduction of previously activated enzymes during repeated cannulation, bacterial contamination and thermal injury from endoscopic sphincterotomy have been implicated as triggering factors that initiate the sequential cascade of pancreatic autodigestion and release of proinflammatory cytokines leading to acute pancreatitis. Recovery from post-ERCP pancreatitis is usually rapid when the injury is confined to the pancreas. However, systemic production of inflammatory mediators may lead to the development of more serious manifestations including multiorgan failure.

A wide range of pharmacological agents has been tested in experimental and clinical trials, but the results have been largely disappointing. Several drugs are discussed in this review, but only somatostatin and gabexate (gabexate mesilate) have consistently shown a moderate beneficial effect. In clinical trials, both gabexate and somatostatin appear equally effective in reducing the incidence of pancreatitis by two-thirds compared with controls. However, both drugs need to be given by continuous infusion for about 12 hours and this makes them less cost-effective than conventional treatment. One potential strategy is to reserve these drugs for high-risk patients undergoing ERCP. Preliminary studies have shown encouraging results with nitroglycerin, antibacterials and heparin. However, these observations need to be corroborated in a rigorous fashion in large, randomised, double-blind, controlled trials. If these drugs are found to be effective in further trials, it may become cost-effective to use them routinely for the prevention of post-ERCP pancreatitis. Despite the theoretical benefits, interleu-

kin-10 has not shown a consistent benefit in clinical trials. It is probable that other cytokine inhibitors or modulators may become available for future trials to prevent pancreatitis or more probably, to reduce the severity of pancreatitis. Further research also should focus on developing newer molecules or the use of a combination of currently available drugs to prevent pancreatitis in high-risk patients undergoing therapeutic ERCP procedures.

Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopic technique that has been in use for more than 30 years for imaging biliary and pancreatic ducts. ERCP is a valuable technique in the management of pancreatic and biliary diseases because it allows the physician to perform therapeutic procedures (e.g. gallstone extraction, biliary drainage, stent placement) at the time of diagnosis.[1,2] In experienced hands, the success rate of ERCP is around 95% but it is associated with a serious complication rate of 3–5%. The major complications associated with ERCP include acute pancreatitis, bleeding and perforation. Of these, acute pancreatitis is a cause for major concern because of the associated morbidity and occasional mortality.[3,4] A key pathological feature of acute pancreatitis is an inflammatory reaction, which may begin as a localised process with a propensity to amplify and induce a generalised systemic inflammatory response. In a significant subset of patients, oedema of the pancreas is associated with extensive local and systemic effects including features of multiple organ failure, which is ultimately responsible for the associated morbidity and mortality. Gallstones and alcohol are responsible for approximately 80% of acute pancreatitis episodes in the US. Besides post-ERCP pancreatitis, other less common predisposing conditions include hyperlipidaemia, medications, infections, trauma, hypercalcaemia, ischaemia and toxins. Irrespective of the cause, the symptoms of acute pancreatitis are somewhat similar, but the severity and complications may vary depending on the cause.[5-7]

This review of pharmacological prevention of post-ERCP pancreatitis aims to be selective, including the most important studies, rather than exhaustive.

## 1. Incidence and Risk Factors for Post-Endoscopic Retrograde Cholangiopancreatography (ERCP) Pancreatitis

Asymptomatic hyperamylasaemia is seen in about 25–75% of patients after ERCP and it is considered clinically insignificant.[8,9] Data from recent prospective studies suggest that the frequency of clinically significant pancreatitis after ERCP may range between 1–13.5%, and it is more common after therapeutic procedures such as sphincterotomy or balloon dilatation and diagnostic procedures such as biliary or pancreatic manometry.[10,11] The severity of acute post-ERCP pancreatitis may vary from very mild to extremely severe disease with multiple organ failure and fatal outcome.

A combination of several technical and patient factors may play a role in the onset of pancreatic injury after ERCP. Important technical factors include papillary trauma and oedema caused by repeated probing with a cannula or guide wire (especially in patients where biliary or pancreatic cannulation is difficult), hydrostatic injury of the pancreatic acinar cells caused by excessive injection of hyperosmolar contrast-material, pancreatic sphincterotomy, precut sphincterotomy and balloon dilation of the biliary sphincter.[12,13] Experience of the endoscopist is also one of the important factors

that may determine the incidence of post-ERCP pancreatitis. Patient characteristics that increase the risk of post-ERCP pancreatitis are female gender, age >55 years, normal serum bilirubin, suspected sphincter of Oddi dysfunction, non-dilated bile duct and previous post-ERCP pancreatitis. The mechanism by which these variables predispose to pancreatitis after ERCP remains unclear.[12,13]

Since ERCP is widely performed, it is likely that both diagnostic and therapeutic ERCP will be performed by endoscopists with varying expertise. However, recent developments in other imaging modalities, including magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS), may reduce the need for diagnostic ERCP. In addition, use of pancreatic stenting in carefully selected patients and use of nonionic, low osmolarity contrast media may reduce the incidence or severity of pancreatitis.[14] A detailed discussion on 'patient and operator' factors is beyond the scope of this review, which focuses on pharmacological prevention of post-ERCP pancreatitis.

## 2. Pathophysiology of Acute Pancreatitis

A great deal of information, based on animal models, has emerged over the past few years on the early events in the pathogenesis of acute pancreatitis. It is now accepted that various causes of acute pancreatitis converge at a common point that initiates a cascade of pathological events resulting in acute pancreatitis. However, the cascade of events is complex and how each event leads to the next is poorly understood. The central pathophysiological mechanism of acute pancreatitis is believed to be intracellular activation of digestive enzymes.[14] Intracellular activation of trypsinogen is thought to be an early and critical event in pathogenesis of acute pancreatitis. This in turn leads to premature activation of other zymogens causing injury of the acinar cell. The predominant mechanism for the activation of trypsinogen in the acinar cell is unclear. Autoactivation of trypsinogen or activation by co-localisation of trypsinogen with cathepsin B (a lysosomal hydrolase known to activate trypsinogen) in cytoplasmic vacuoles have been proposed as potential mechanisms.[15,16]

Activation of trypsinogen leads to a cascade events including oxidative stress, nuclear translocation of nuclear factor kappa B (NFκB) and subsequent generation and release of inflammatory mediators such as tumour necrosis factor (TNF), interleukin (IL)-1, platelet activating factor (PAF), bradykinin, nitric oxide, etc., by the acinar cell.[17] This results in the recruitment of more cytokine producing polymorphonuclear leucocyte (PMN) cells and macrophages. The end result is an overproduction of inflammatory mediators, amplification of the inflammatory reaction and apoptosis of pancreatic cells.[18,19] These inflammatory mediators may also spill over into the general circulation producing a systemic inflammatory response.

TNF and IL-1 are the key proinflammatory cytokines and, in addition, these cytokines play an important role in the apoptosis of acinar cells. Most of the IL-1 and TNF are produced after the onset of acute pancreatitis by the invading leucocytes, in amounts several orders of magnitude higher than then their concentration in the serum. However, only a proportion of patients with acute pancreatitis will demonstrate IL-1 or TNF in the serum because of rapid clearance of these cytokines by the liver. The detection of TNF in the systemic circulation during acute pancreatitis suggests very severe disease and portents a poor prognosis. IL-1 and TNF are also produced in other organs, such as the liver, spleen and lungs, with the production in the pancreas preceding that in the distant sites. These cytokines are actively involved in the propagation of pancreatic injury and may ultimately determine the severity of pancreatitis. An overwhelming amount of evidence also suggests that IL-1 and TNF are responsible for the induction of systemic consequences of pancreat-

ic injury including fever, shock, tissue hypoperfusion, metabolic acidosis, acute respiratory distress syndrome (ARDS) and cardiac dysfunction. In experimental models of acute pancreatitis, animals that lack IL-1-receptor, TNF-receptor or both had improved survival compared with wild-type animals. Moreover, knockout animals that lack TNF receptors showed no apoptosis during acute pancreatitis. Similarly, animals given cytokine inhibitors have shown a favourable outcome.[14,20-22]

IL-1 and TNF are also the primary inducers of IL-6 and IL-8. Numerous studies have found a strong correlation between the circulating levels of IL-6 and IL-8 with the severity of acute pancreatitis, complications including multiorgan failure and mortality. In the future, routine measurement of IL-6 after the onset of acute pancreatitis may help in early identification of patients who need more aggressive resuscitation and monitoring.[23,24] In addition to the above-mentioned cytokines, local production of PAF by pancreatic acinar cells and the invading leucocytes, macrophages and platelets enhances local exocrine secretion, and increases both local and systemic inflammatory responses. PAF is a key mediator in PMN cell activation, chemotaxis, superoxide release and degranulation, and may also play a role in initiating the production of other inflammatory mediators such as prostaglandins and leukotrienes. In experimental models of acute pancreatitis, pretreatment with PAF antagonists has been shown to ameliorate the severity and complications of acute pancreatitis and reduce mortality.[25,26] All of these cytokines (TNF, IL-8, IL-6 and PAF) are involved in expression and up regulation of cell adhesion molecules on both leucocytes and vascular endothelium, which in turn facilitates neutrophil adhesion and migration into the tissues where they subsequently differentiate, release cellular enzymes and propagate the inflammation. In animal models of acute pancreatitis, antagonism of leucocyte adhesion and migration by the use of antibodies or by neutrophil depletion has been shown to reduce the severity of pancreatic damage.[27,28]

The inflammatory cells infiltrating the pancreas also produce IL-10, a major anti-inflammatory cytokine. IL-10 inhibits the production of proinflammatory cytokines by activated PMN cells and macrophages. In experimental models of acute pancreatitis, administration of IL-10 before or after the induction of pancreatitis attenuates the severity of pancreatitis and reduces pancreatic necrosis. One of the suggested mechanisms of action of IL-10 is the inhibition of local release of TNF by macrophages. The production and release of IL-10 occurs in multiple organs even when acute pancreatitis is limited to the pancreas. IL-10 also regulates the pancreatic, lung and liver production of TNF, and attenuates pancreatic inflammation and multiple organ failure associated with severe pancreatitis. IL-10 may exert its beneficial effects by down regulating the expression of cell adhesion molecules (intercellular adhesion molecule [ICAM]-1 and vascular cell adhesion molecule [VCAM]-1) and controlling the release of IL-1and IL-8.[29,30]

Other mediators that are being increasingly recognised for their role in acute pancreatitis and deserve a brief mention are substance P and the complement component C5a. Substance P, a well-known mediator of pain, is proinflammatory neuropeptide that is released in many tissues from the nerve ending. It acts via membrane-bound natural killer (NK)-1 receptors and play an important role acute pancreatitis. Knockout animals that are deficient in NK1 receptors are protected against pancreatitis and the associated lung injury, and those deficient in inhibitors of substance P are more susceptible to pancreatitis and associated lung injury. C5a is generated from C5 as a part of both the classical and the alternate pathways of complement activation. In experimental models, animals that do not express C5 or lack C5a receptors exhibit more severe acute pancreatitis and associated lung injury

than wild-type controls. The mechanisms by which substance P and C5a exert their effects are still rudimentary.[31,32] The major cytokine mediators of acute pancreatitis and their effects are summarised in table I.

It is important to remember that the cascade of events that lead to pancreatitis usually take place within a short period of time (in minutes) and this may explain why cytokine modulators have to be given prophylactically to prevent or reduce the ERCP-induced pancreatitis.

## 3. Pancreatitis After ERCP

The characteristic clinical features of acute pancreatitis, irrespective of aetiology, include acute epigastric or left side abdominal pain often radiating to the back, nausea, vomiting and anorexia. On physical examination, patients may exhibit marked tenderness in the epigastrium with or without guarding, tachycardia, fever, tachypnea or hypovolaemia depending on the severity of pancreatitis. Serum amylase and lipase levels are often markedly elevated, but the levels may not always correlate with the severity of pancreatitis. Recovery from post-ERCP pancreatitis is rapid when the injury is confined to the pancreas. However, systemic production of inflammatory mediators may lead to the development of more serious manifestations especially multiorgan failure. There is generally a delay of 3–7 hours between the injury to the pancreas caused by ERCP and the onset of symptoms. Serum lipase and amylase levels increase within the first 4 hours and return to their normal values within 72 hours in most patients with mild pancreatitis. Acute pancreatic injury is associated with an increase in IL-6 within 12–48 hours followed by an increase in C-reactive protein (CRP) 24–48 hours later. IL-6 and CRP levels usually peak at 48 hours and 72 hours, respectively. Patients with severe pancreatitis show an earlier rise in IL-6 and CRP levels, in addition to a higher peak, compared with those who have mild pancreatitis. Similarly, a higher serum IL-1 and IL-8 level immediately after the onset of injury is predictive of the severity of post-ERCP pancreatitis.[33,34] This may imply that the severity of the pancreatitis is set very early in the course of this disease and, hence, the evolution of acute pancreatitis may be predictable. Moreover, these findings suggest that drugs aimed at preventing or modifying ERCP-induced pancreatitis must be administered early, preferably before the ERCP, to be beneficial.[35]

**Table I.** Inflammatory mediators and their effects

| Cytokine mediator | Activity | Systemic effects |
|---|---|---|
| TNF | Proinflammatory, leucocyte activation, induces other mediators | ARDS, shock |
| IL-1 | Proinflammatory, leucocyte activation, induces other mediators | ARDS, shock |
| IL-6 | Leucocyte activation | Acute phase response, stimulates synthesis of C-reactive protein |
| IL-8 | Leucocyte activation and chemotaxis | |
| PAF | Leucocyte activation and chemotaxis | ARDS, shock |
| IL-10 | Anti-inflammatory, inhibits production of proinflammatory cytokines IL-1 and TNF | Attenuates pacreatic and lung injury, maintains homeostasis |

**ARDS** = acute respiratory distress syndrome; **IL** = interleukin; **PAF** = platelet activating factor; **TNF** = tumour necrosis factor.

## 4. Pharmacological Agents for the Prevention of Post-ERCP Pancreatitis

Historically, every pharmaceutical agent shown to be effective in preventing post-procedure pancreatitis has met with scepticism as initial favourable results have invariably been followed by contradictory reports. Currently, there is no proven therapy to prevent ERCP-induced pancreatitis. The ideal prophylactic agent would have the following characteristics: (i) be effective in majority of patients; (ii) be inexpensive; (iii) able to be administered on the day of the procedure, and preferably 30–60

minutes before the procedure; (iv) not require prolonged administration after the procedure; and (v) have no effects on the sphincter of Oddi motility. The search for such an ideal agent for the prevention of pancreatic injury after ERCP has been ongoing since the beginning of ERCP itself. Although a wide range of pharmacological agents have been tested in experimental and clinical trials, the results have been largely disappointing. Several drugs are discussed in this review; however, only somatostatin and gabexate (gabexate mesilate) have consistently shown a moderate beneficial effect.

### 4.1 Somatostatin

Somatostatin is a peptide hormone which is present in the human body in two molecular forms: somatostatin-14 and somatostatin-28 (consisting of 14 and 28 amino acids, respectively). It exerts diverse biological effects through interaction with five specific subtypes of somatostatin receptors in its target tissues. Since the half-life of somatostatin is 1.1–3 minutes, to be effective, continuous intravenous administration of somatostatin is necessary. Both somatostatin-14 and somatostatin-28 bind with a high affinity to all somatostatin receptors subtypes.[36] Somatostatin is a potent inhibitor of pancreatic secretion and is the most extensively studied agent for the prophylaxis of post-ERCP pancreatitis. The efficacy of somatostatin in preventing post-ERCP pancreatitis may be due to its multiple effects, including inhibition of exocrine pancreatic secretion, reduction of sphincter of Oddi contractions, modulation of cytokine cascade and also possibly cytoprotection. The clinical utility of somatostatin for prevention of post-ERCP pancreatitis has been demonstrated by several controlled trials; however, in many of these studies sample size was not sufficient to show a significant beneficial effect.

Poon et al.[37] performed a prospective, randomised, double blind, placebo-controlled study in 220 patients to evaluate the effectiveness of somatostatin in preventing post-ERCP pancreatitis. Somatostatin infusion was started 30 minutes before ERCP and continued for 12 hours after the procedure. The frequency of clinical pancreatitis was significantly lower in patients given somatostatin compared with those receiving placebo (3% vs 10%). In addition, there was a significant decrease in the frequency of post-ERCP abdominal pain requiring analgesia with the use of somatostatin. The authors concluded that prophylactic treatment with somatostatin reduced the frequency of post-ERCP pancreatitis.

Andriulli and colleagues[38] performed a meta-analysis including 12 clinical trials on the use of somatostatin. These studies included 321 patients treated with somatostatin and 325 controls. Acute pancreatitis developed in 5.6% of patients receiving somatostatin and 13.5% of controls ($p < 0.001$, odds ratio [OR] 0.38). Post-procedural increase of serum amylase levels was noted in 44.9% of somatostatin recipients and 55.0% of controls ($p = 0.008$). Thirteen percent of those receiving somatostatin developed abdominal pain compared with 31.6% of controls ($p < 0.001$). The number of patients who had to be treated with somatostatin to prevent one single episode of acute pancreatitis was 13. In this meta-analysis, somatostatin infusion was associated with improvements in all three outcomes including, acute pancreatitis, hyperamylasaemia and pancreatic pain.[38]

The disadvantage of using somatostatin in all patients who undergo ERCP is the need for a continuous 12-hour intravenous infusion and, hence, overnight hospitalisation. This increases the cost of the procedure and makes it prohibitive for routine use. In a recent study, Andriulli et al.[39] examined the efficacy of short-term infusion (30 minutes before and 2 hours after ERCP) of somatostatin and found that it was ineffective. The findings of this study, as well as other previous studies, suggest that somatostatin needs to be given over 12-hour period to be effective. Selective use of 12-hour infusion of so-

matostatin in high-risk patients is likely to be more cost-effective, but this needs to be investigated in controlled trials.

### 4.2 Octreotide

Octreotide is the long-acting octapeptide analogue of somatostatin. Like somatostatin, it inhibits basal and stimulated pancreatic secretion, and exerts its effects through interaction with somatostatin receptor. However, octreotide binds with a high affinity only to somatostatin receptor types 2 and 5.[36] Unlike somatostatin, octreotide may stimulate and increase the pressure of sphincter of Oddi. Octreotide can be administered either subcutaneously or intravenously. In addition, a slow-release intramuscular depot preparation is currently available. Clinical trials have not shown a consistent benefit with octreotide and its use for the prevention of post-ERCP pancreatitis remains controversial.

In a large multicentre, prospective, controlled trial (2102 patients from 11 centres), Tulassay and colleagues[40] studied the efficacy of octreotide for the prevention of pancreatitis after ERCP and endoscopic sphincterotomy. In this study, patients in the treatment arm received subcutaneous octreotide 0.1mg before and 45 min after ERCP, but the prophylactic use of octreotide did not reduce the frequency of post-ERCP pancreatic injury.[40] Similar conclusions were drawn by Testoni et al.[41] in a multicentre, randomised, controlled trial in 114 patients. In this study, subcutaneous octreotide 200μg was administered 8 hourly, starting 24 hours before the ERCP. Post-procedure pancreatitis occurred in 12% of patients treated with octreotide and 14.3% of controls. Similarly, the two groups showed no significant differences in the incidence or severity of pancreatitis. In a three-arm, multicentre, randomised, controlled trial, Manolakopoulos et al.[42] compared the efficacy of subcutaneous octreotide 100μg with intravenous hydrocortisone 100mg or placebo for the prevention of post-ERCP pancreatitis in 354 patients. All medications were administered approximately 30 minutes before the procedure. The frequency of pancreatitis after ERCP and the mean length of hospitalisation were similar in all three groups. The results of this trial indicated that neither octreotide nor hydrocortisone prevented ERCP-induced pancreatitis. Finally, Andriulli et al.[38] performed a meta-analysis on ten studies that used octreotide for the prevention of post-ERCP pancreatitis. Data were derived from 423 patients treated octreotide and 430 controls. Outcome measures evaluated were the incidence of acute pancreatitis, hyperamylasaemia and pancreatic pain. Acute pancreatitis developed in 7.6% of patients who received prophylactic octreotide and 5.6% of controls ($p = 0.2$). Although octreotide was associated with a reduced risk of post-ERCP hyperamylasaemia, it had no effect on acute pancreatitis and pain.[38]

These studies showed that octreotide, despite the ease of administration and direct costs lower than somatostatin, was ineffective as a prophylactic agent for the prevention of post-ERCP pancreatitis at the dosages used. It is possible that the reduction in pancreatic secretion by octreotide may be offset by the inhibition of outflow caused by an increase the pressure of the sphincter of Oddi. This may be one of the explanations for the discrepancy in the efficacy between somatostatin and its long acting analogue octreotide. The route of administration and the dosage are other potential reasons.

### 4.3 Gabexate

Gabexate is a synthetic, nonantigenic, 417-dalton, protease inhibitor. It has a half-life of 55 seconds, is widely distributed and is eliminated in inactive form by the kidneys. The parent compound of gabexate is aprotinin, a 6513-dalton molecule. Gabexate has effects on trypsin, kallikrein and plasmin, thrombin, phospholipase A2 and C1 esterase. Studies in experimental animals and humans have demonstrated that prophylactic administration of gabex-

ate prevented acute pancreatitis.[43-45] In addition, in both animals and humans, gabexate has an inhibitory action on the sphincter of Oddi.[46]

In a multicentre, randomised, double-blind, placebo-controlled study, Cavallini et al.[47] examined the efficacy of gabexate for the prevention of post-ERCP pancreatitis in 435 patients. Patients received a continuous intravenous infustion of gabexate 1g starting 30–90 minutes before the ERCP and for 12 hours after the procedure. In this study, patients receiving gabexate had a lower incidence of acute pancreatitis (2% vs 8%) than those receiving placebo. In addition, those patients in the gabexate group who developed pancreatitis had mild pancreatitis that resolved with medical measures only. In contrast, one-third of patients with acute pancreatitis in the placebo group developed necrotising pancreatitis.[47]

In a meta-analysis of six studies (duration of infusion varied significantly between these studies), Andriulli et al.[38] examined the incidence of acute pancreatitis, hyperamylasaemia and pancreatic pain in 311 patients who received gabexate and 369 controls. Acute pancreatitis developed in 1.6% of patients in the gabexate group and 6.5% of controls (OR 0.27, p = 0.001). The incidence of hyperamylasaemia and pancreatic pain was also significantly lower in the gabexate group. Thus, gabexate was associated with significant improvements in all three outcomes. This meta-analysis showed that 27 patients had to be treated with gabexate to prevent one single episode of acute pancreatitis. The adverse effects of gabexate are generally mild, and included nausea, vomiting, abdominal discomfort, headache and allergic reactions.[37,47]

However, like somatostatin, gabexate is very expensive as a prophylactic agent since it needs to be given as an infusion for 12 hours after ERCP, which requires overnight hospitalisation. Since the majority of ERCPs are performed on an outpatient basis, the costs (cost of drug + hospitalisation) associated with gabexate infusion prohibit its routine use. A recent study examined the comparative efficacy of short-term infusion (30 minutes before and 2 hours after ERCP) of somatostatin, gabexate and placebo, and found similar rates of pancreatitis (11.5%, 8.1% and 6.5%, respectively) suggesting that both drugs were ineffective when used in this fashion in high-risk patients.[39] Moreover, in the same report, the authors performed another meta-analysis that indicated that short-term infusion (<4 hours) of gabexate may not reduce the incidence of post-ERCP pancreatitis.

These trials show that both gabexate and somatostatin are equally effective when used as a 12-hour infusion. Both drugs reduce the incidence of post-ERCP pancreatitis to one third that of control groups. However, gabexate is less cost-effective than somatostatin and, unlike somatostatin, gabexate has not been approved for clinical use in many countries including the US. In those countries where gabexate is available for clinical use, it should probably be reserved for those patients at greatest risk of developing post-ERCP pancreatitis.[48]

### 4.4 Interleukin-10

As mentioned in section 2, IL-10 is a major anti-inflammatory cytokine that can limit the severity of acute pancreatitis in experimental models. In a randomised, double-blind, placebo-controlled, single centre study in 137 patients, Deviere et al.[49] evaluated the effectiveness of IL-10 for the prevention of post-ERCP pancreatitis. In this study, recombinant human IL-10 was given as a single intravenous injection at a dose of 4 or 20 mg/kg 30 minutes before the procedure. The incidence of pancreatitis was significantly higher in the placebo group than the group receiving IL-10 (24% vs 9%, p = 0.04). Two episodes of severe pancreatitis were observed in the placebo group and none in IL-10 group. Moreover, IL-10 was well tolerated without any adverse effects. However, no significant differences

in plasma IL-6, IL-8, TNF or CRP levels were observed.

More recently, Dumot et al.[50] conducted a randomised, double-blind, placebo-controlled study in 200 patients to evaluate the safety and efficacy of low dose IL-10 for the prevention of ERCP-induced pancreatitis. A single dose of recombinant human IL-10 8 μg/kg was given intravenously 15 minutes before the procedure. Unlike the previous study, the incidence of pancreatitis was not significantly different in patients who received IL-10 (11% vs 9%, p = 0.7) compared with those who received placebo. This study showed that IL-10 at the 8 μg/kg dose was not effective in reducing the incidence or severity of ERCP-induced pancreatitis.

Larger trials and, more importantly, dose optimisation studies are necessary to identify the role of IL-10 as a prophylactic agent for prevention of post-ERCP pancreatitis. Since IL-10 is effective for 24 hours after a single intravenous injection, hospitalisation is not necessary for patients undergoing therapeutic ERCP on an ambulatory basis. Therefore, IL-10, if its efficacy is proven in larger trials, is potentially more cost-effective than either gabexate or somatostatin as prophylactic agent for the prevention of post-ERCP pancreatitis.[49] On the basis of limited data, IL-10 cannot be recommended for the prevention of post-ERCP pancreatitis outside clinical trials.

### 4.5 Nitroglycerin

Nitroglycerin (glyceryl trinitrate) is a rapid and short acting organic nitrite used extensively for cardiovascular diseases. Nitroglycerin has a powerful relaxant effect of smooth muscles. Sublingual administration of nitroglycerin produces effects within one to two minutes which can last up to 30 minutes. Nitroglycerin can produce a reduction in the basal tone of the sphincter of Oddi and decrease the resistance to bile flow.[51,52] This dilating effect of nitroglycerin on the sphincter of Oddi can facilitate cannulation of the common bile duct and help remove small gallstones from the bile ducts through intact papillae. The effects of nitroglycerin on the sphincter of Oddi muscle last for approximately 15 minutes.

In a randomised, double-blind, placebo-controlled study, Sudhindran et al.[53] evaluated the effect of prophylactic treatment with nitroglycerin 2mg administered sublingually 5 minutes before ERCP in 186 patients who presented for elective ERCP. The incidence of pancreatitis was lower in the nitroglycerin group than the placebo group (8% vs 18%, p = 0.05) but mean serum amylase values were similar in the two groups. More than 50% patients who received nitroglycerin had significant hypotension requiring intravenous infusion of crystalloids. Although prophylactic treatment with nitroglycerin decreased the incidence of pancreatitis following ERCP, the protective effect was highest in the diagnostic ERCP group and in the group in which cholangiography alone was performed.[53]

Patients who undergo diagnostic ERCP alone are generally considered to have a low risk for post-procedure pancreatitis. Moreover, diagnostic ERCP is being supplanted by other noninvasive technologies (e.g. MRCP) in many centres. Although the ease of administration and cost considerations make nitroglycerin an attractive prophylactic agent, the enthusiasm for this drug should be reserved until more studies corroborate these favourable results. In addition, benefit should be shown in patients who are at an increased risk for developing post-ERCP pancreatitis.

### 4.6 Corticosteroids

The anti-inflammatory properties of corticosteroids may have a beneficial effect in patients with acute pancreatitis.[54] In addition, in animal models, corticosteroids have shown indirect inhibitory effects on trypsin activation and phospholipase $A_2$,

which in turn may reduce the severity of acute pancreatitis.[55,56]

In a retrospective study of 824 patients who were given oral or intravenous corticosteroids before ERCP for iodine sensitivity, the incidence of post-ERCP pancreatitis was found to be significantly lower in the group that received corticosteroids compared with those who did not.[57] Moreover, the benefit was more obvious in the corticosteroid group who had undergone therapeutic procedures.[57] However, the enthusiasm generated by this study was dampened by a large, prospective trial that showed no benefit of corticosteroids in preventing post-procedure pancreatitis.[58] In this randomised, double blind study, 535 patients were given hydrocortisone 100mg or placebo by intravenous infusion immediately before ERCP. The incidence of acute pancreatitis was 5.7% in patients treated with hydrocortisone and 4.9% in the placebo group (p = NS).[58] This study clearly showed that prophylactic use of corticosteroids has no role for the prevention of post-ERCP pancreatitis.

### 4.7 Antibacterials

It has been suggested that enteric bacteria may play a role in the pathogenesis of post-ERCP pancreatitis. In experimental animals, antibacterials have shown to reduce the severity of pancreatitis and improve survival.[59-61] In patients with obstructive jaundice and pseudocysts, intravenous antibacterials are given routinely prior to ERCP to prevent biliary and pancreatic sepsis. However, there are only limited data on the role of antibacterial prophylaxis for the prevention of post-ERCP pancreatitis.

In a prospective, randomised, controlled study of 321 patients, Raty et al.[62] showed that ceftazidime 2g intravenously 30 minutes before ERCP significantly reduced the incidence of post-ERCP pancreatitis. The incidence of pancreatitis in the group that received antibacterial prophylaxis was 2.5% compared with 9.4% in the group that did not (p = 0.009).[62] This observation merits further confirmation. Moreover, if antibacterials are found to be effective in a larger study, the subgroup that benefits most from antibacterial prophylaxis should be identified. On the basis of the current evidence, routine use of antibacterial prophylaxis before ERCP cannot be recommended.

### 4.8 Heparin

In animal models of acute pancreatitis, heparin improves pancreatic microcirculation, inhibits pancreatic proteases, and significantly improves the course and severity of acute pancreatitis. Heparin has been shown to inhibit the proinflammatory effects of TNF and IL-1. It also inhibits the interactions between cell adhesion molecules expressed on leucocytes, platelets and endothelial cells. The anti-inflammatory effect of heparin does not depend on its anticoagulant properties, as it can be observed even at concentrations much lower than those recommended for therapeutic anticoagulation. In addition, unfractionated heparin may be a more potent inhibitor of inflammation than low molecular weight heparin.[63,64]

In a prospective, nonrandomised study of 805 patients, heparin (both low molecular weight and unfractionated) was administered to 268 (32.9%) patients for various clinical reasons. The frequency of acute pancreatitis was significantly lower in the heparin group than the control group, 3.4% vs 7.9% (p = 0.005), and this effect could not be attributed to other known or suspected confounders.[65] Moreover, heparin did not increase the risk of haemorrhage after endoscopic sphincterotomy.[65] Despite the promising results of this nonrandomised study, prophylactic administration of heparin cannot be recommended at present and further prospective, randomised, controlled studies are needed to verify these observations.

### 4.9 Nifedipine

Nifedipine is a dihydropyridine calcium channel antagonist with antianginal and antihypertensive properties. Nifedipine is a potent relaxer of smooth muscles and acts by reducing intracellular calcium concentrations. Cannulation-induced sphincter of Oddi spasm with a temporary pancreatic duct obstruction is one possible mechanism for post-ERCP pancreatitis. Nifedipine is known to relax the sphincter of Oddi, thus possibly inhibiting or reducing pancreatic injury after ERCP ± endoscopic sphincterotomy.[66,67]

In a randomised, double-blind, placebo-controlled study, 166 adult patients undergoing ERCP with or without endoscopic sphincterotomy were randomised to receive either nifedipine 20mg three times daily (i.e. 8 hourly intervals) or placebo during the day of the procedure.[68] The first dose was given 3–6 hours before the procedure and all patients received antibacterials before ERCP. The incidence of acute pancreatitis was similar in the nifedipine and placebo group (4% in each group). Necrotising pancreatitis developed in 2% of patients in the nifedipine group and 1% in the placebo group. There was also no difference in the incidence of pain and hyperamylasaemia between the two groups.[68] This study showed that despite its potential inhibitory effect on sphincter of Oddi motility, nifedipine has no role for the prevention of post-ERCP pancreatitis.

### 4.10 Other Agents

In addition to the drugs already discussed in this section, various other pharmacological agents have been investigated for the prevention of post-ERCP pancreatitis, including calcitonin, glucagon, allopurinol and low osmolality contrast agents.[10,69-71] These agents have either failed to prevent pancreatitis or produced inconsistent results in clinical trials.

There is experimental and clinical evidence to suggest that loxiglumide (a cholecystokinin-A-receptor antagonist) may be beneficial in the management of acute pancreatitis or painful attacks of chronic pancreatitis.[72-74] However, to our knowledge, there have been no studies to determine whether prophylactic use of this drug can prevent or reduce the severity of post-ERCP. A summary of currently available drugs is provided in table II.

## 5. Conclusion

Specific therapy for the prevention of post-ERCP pancreatic injury has eluded therapeutic endoscopists for decades. Although at present there are no drugs in widespread use for prevention of post-ERCP pancreatitis, there is evidence to suggest that somatostatin and gabexate are probably effective in reducing the incidence and severity of post-ERCP pancreatitis. However, in addition to being expensive and cumbersome to administer, these drugs are not currently approved or available for this indication. Preliminary studies show encouraging results with nitroglycerin, antibacterials and heparin. How-

**Table II.** Efficacy of drugs to prevent post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis

| Drug | Route of administration | Evidence of efficacy | Cost |
|---|---|---|---|
| Somatostatin | IV infusion for 12h | +++ | $$$ |
| Octreotide | SC, IV or IM | – | $$ |
| Gabexate | IV infusion for 12h | +++ | $$$$ |
| Interleukin-10 | Single IM injection | ± | $$ |
| Nitroglycerin | Sub-lingual | + | $ |
| Corticosteroids | IV injection or IM | – | $ |
| Antibacterials | IV injection | + | $ |
| Heparin | SC | ± | $ |
| Nifedipine | IM | – | $ |
| Other agents | – | – | $ |

**IM** = oral; **IV** = intravenous; **Other agents** = calcitonin, allopurinol, glucagon, low osmolality contrast agents etc; **SC** = subcutaneous; **–** indicates no benefit; ± indicates conflicting data; **+** indicates possible but minimal data; **+++** indicates probable; **$** indicates least expensive; **$$$$** indicates most expensive (cost is based on the cost of drugs and hospitalisation, and does not take into consideration the cost of managing patients who develop post-ERCP pancreatitis).

ever, these observations need to be corroborated in a rigorous fashion in large, randomised, double-blind, controlled trials using standardised methodology and definitions. If these drugs are found to be effective in further trials, it may become cost-effective to use them routinely for the prevention of post-ERCP pancreatitis. Despite the theoretical benefits, two randomised, controlled trials produced conflicting results with anti-inflammatory cytokine IL-10. It is probable that other cytokine inhibitors or modulators may become available for future trials to prevent pancreatitis or, more probably, to reduce the severity of pancreatitis. Further research also should focus on developing newer molecules or use of a combination of currently available drugs to prevent pancreatitis in high-risk patients undergoing therapeutic ERCP procedures.

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