Antisecretory Agents for Prevention of Post-ERCP Pancreatitis: Rationale for Use and Clinical Results

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Summary

Acute pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP). Over the past decade, there has been notable research on the use of various prophylactic agents in preventing post-ERCP pancreatitis. The most widely investigated drug is the antisecretory agent somatostatin and its analogue octreotide. Both agents are potent inhibitors of exocrine secretion of the pancreas, which plays an important role in the pathogenesis of acute pancreatitis by causing autodigestion of pancreas. In addition, somatostatin and octreotide appear to have anti-inflammatory and cytoprotective effects, both of which may be protective against post-ERCP pancreatitis. Furthermore, somatostatin has been shown to relax the sphincter of Oddi, whereas octreotide increases the basal pressure of the sphincter. Several randomized controlled trials have evaluated the efficacy of somatostatin and octreotide in reducing post-ERCP pancreatitis. The results of these trials vary due to different patient populations and experimental designs. Overall, the available evidence suggests that somatostatin reduces the incidence of post-ERCP pancreatitis, whereas octreotide does not. Whether the difference in efficacy between the two drugs is related to their differential effects on sphincter of Oddi motility or is due to other reasons remains unclear. Although there is some evidence supporting the use of somatostatin in reducing the frequency of post-ERCP pancreatitis, it is widely agreed that generalized treatment of all patients undergoing ERCP with prophylactic somatostatin may not be cost-effective. Further studies should focus on the elucidation of the most cost-effective dosage regimen of somatostatin and its efficacy in patients at high risk for post-ERCP pancreatitis.

Introduction

Acute pancreatitis is the most common complication after endoscopic retrograde cholangiopancreatography (ERCP). The reported frequency of post-ERCP pancreatitis varies from 1 to 40% due to diverse definitions of post-ERCP pancreatitis and different methods of data collection [1]. More accurate data were obtained from prospective studies with serial measurement of serum amylase and assessment of abdominal pain after ERCP as compared to retrospective studies. The incidence of post-ERCP pancreatitis ranges from 5 to 10% in prospective studies [2, 3, 4, 5, 6]. However, even in prospective studies, the definition of ERCP varies widely. In a consensus paper published in 1991, post-ERCP pancreatitis was defined as a rise of the serum amylase level 3 times above normal and pain persisting for more than 24 hours after the procedure [7]. However, this has not gained
universal acceptance, and the definitions of acute pancreatitis have ranged from 2 to 5 times above normal levels in serum amylase and pain from 4 to 24 hours after ERCP in various subsequent studies [3, 4, 5, 6, 8]. Despite technical improvements in recent years and increased experience of endoscopists with ERCP procedures, the incidence of post-ERCP pancreatitis has not decreased [2]. Although post-ERCP pancreatitis seldom results in death, it is the commonest reason for prolonged hospital stay after ERCP [7]. Several studies have investigated the risk factors of post-ERCP pancreatitis, which include sphincter of Oddi dysfunction, nondilated bile duct, previous post-ERCP pancreatitis, difficult cannulation, repeated pancreatic duct injections, pancreatic duct acinarization, endoscopic sphincterotomy and precut technique of sphincterotomy [2, 5, 7, 9, 10, 11]. Except for patients with well-defined risk factors such as sphincter of Oddi dysfunction, the majority of cases of post-ERCP pancreatitis are related to technical factors that may be difficult to avoid. As a result, attention has been focused in recent years on the use of pharmacological agents to prevent post-ERCP pancreatitis. Somatostatin and octreotide are the two agents that have been investigated most widely for their prophylactic effect on post-ERCP pancreatitis.

Rationale for the Use of Antisecretory Agents

Somatostatin is a naturally occurring peptide found in considerable amounts in the gastrointestinal tract, including the pancreas. Somatostatin has a wide range of effects, mainly inhibitory, in the gastrointestinal tract. In the pancreas, somatostatin affects the exocrine function both directly, by reducing the secretion of digestive enzymes, and indirectly, by inhibiting secretin and cholecystokinin production [12]. Octreotide is a synthetic analogue of somatostatin with a similar spectrum of actions but a longer biological half life [13]. Octreotide is also a potent inhibitor of pancreatic enzyme secretions.

Although the initiating pathophysiological mechanism of acute pancreatitis remains unclear, the disease is characterized by the destruction of the gland and its peripancreatic fat by enzymes secreted by the pancreas itself. It has been demonstrated in an animal model that stimulation of exocrine pancreatic secretion leads to further deterioration of acute pancreatitis [14]. Both somatostatin and octreotide have been shown to have a protective effect on experimental acute pancreatitis [15, 16]. The use of these drugs for the prevention of post-ERCP pancreatitis is reasonable based on the experimental results.

In addition to their antisecretory effects, there are some other pharmacological actions of somatostatin and octreotide that may be beneficial in the prevention of post-ERCP pancreatitis. Whatever the initial intracellular events, acute pancreatitis is characterized by an early local and systemic inflammatory reaction which is increased by a cascade of cytokines [17]. Somatostatin and octreotide have been demonstrated to modulate the cytokine cascade [18, 19]. An experimental study has suggested that somatostatin may induce apoptosis in pancreatic acinar cells to reduce the inflammatory reaction during acute pancreatitis [20]. A recent study has shown that the use of an anti-inflammatory cytokine, interleukin-10, could reduce the incidence of post-ERCP pancreatitis [21]. The anti-inflammatory action of somatostatin may play a role in the prevention of post-ERCP pancreatitis. Somatostatin and octreotide may also have a cytoprotective effect on pancreatic cells, although the mechanism whereby these agents exert their cytoprotective effect is unknown [16, 22]. Somatostatin is also known to reduce the motility of the sphincter of Oddi [23]. A recent study has demonstrated that somatostatin can relax the sphincter of Oddi in patients with acute non-biliary pancreatitis [24]. Spasms of the sphincter of Oddi and edema of the papilla leading to pancreatic
duct obstruction are possible mechanisms of post-ERCP pancreatitis [1]. Hence, the relaxing effect of somatostatin may be beneficial in the prevention of post-ERCP pancreatitis. In contrast, octreotide increases the contractility of sphincter of Oddi [25], which could be detrimental in acute pancreatitis if activated enzymes are retained in the gland. A study of patients with acute recurrent pancreatitis has shown that administration of octreotide induces a rise in the sphincter of Oddi pressure with possible impairment of biliary-pancreatic outflow [26]. The exact reason for the different physiological effects of somatostatin and octreotide is unknown. It has been postulated that the differential effects of the two agents may be related to the different receptor subtypes present on the inhibitory neural input to the sphincter [27].

Clinical Results of Somatostatin as a Prophylactic Agent for Post-ERCP Pancreatitis

The first study on the effect of somatostatin on post-ERCP pancreatitis was reported by Borsch et al. [28], who found a similar incidence of acute pancreatitis (10%) in 10 patients treated with somatostatin 250 µg/h for 24 hours as compared to another 10 patients treated with placebo. However, the study was not randomized and the sample size was too small. Two subsequent small studies investigated hyperamylasemia after ERCP with the use of somatostatin, with one demonstrating a significant reduction [29], and the other showing no significant difference compared with a control group [30]. Following these preliminary studies, several randomized controlled trials have been published (Table 1). In a randomized trial involving 33 patients, Bordas et al. [31] showed a significant reduction in post-ERCP hyperamylasemia after a single-dose bolus intravenous injection of somatostatin. There was an 11.8% incidence of acute pancreatitis among 17 patients who received a placebo, while no patients in the somatostatin group developed acute pancreatitis. However, the difference in the incidence of pancreatitis in that study was not significant, probably because of the small sample size [31]. In a more recent randomized controlled trial reported by the same authors which involved 160 patients undergoing pancreatography, there was a significant reduction in the incidence of acute pancreatitis among patients who received a bolus intravenous injection of somatostatin in a dose of 4 µg/kg as compared to patients who received a placebo (0% versus 18%) [32]. On subgroup analysis, the difference in the frequency of acute pancreatitis was significant among patients with endoscopic sphincterotomy but not in the group with ERCP alone, suggesting that prophylactic somatostatin may work best in patients at high risk of post-ERCP pancreatitis.

The other randomized trials on the use of somatostatin for prophylaxis of post-ERCP pancreatitis employed continuous infusion of somatostatin for a variable duration ranging from 2 to 26 hours (Table 1). Earlier

<table>
<thead>
<tr>
<th>Study</th>
<th>Total number of patients</th>
<th>Dosage regimen of somatostatin</th>
<th>AP in control group</th>
<th>AP in treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bordas 1988 [31]</td>
<td>33</td>
<td>4 µg/kg bolus</td>
<td>11.8%</td>
<td>0%</td>
</tr>
<tr>
<td>Saari 1988 [33]</td>
<td>39</td>
<td>250 µg/h x 3 h</td>
<td>15.4%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Testoni 1988 [34]</td>
<td>53</td>
<td>250 µg/h x 26 h</td>
<td>19.3%</td>
<td>7.4%</td>
</tr>
<tr>
<td>Guerland 1991 [36]</td>
<td>21</td>
<td>250 µg/h x 13 h</td>
<td>75%</td>
<td>25%</td>
</tr>
<tr>
<td>Persson 1992 [35]</td>
<td>54</td>
<td>300 µg/h x 4 h</td>
<td>17.9%</td>
<td>15.4%</td>
</tr>
<tr>
<td>Bordas 1998 [32]</td>
<td>160</td>
<td>4 µg/kg bolus</td>
<td>10%*</td>
<td>2.5%*</td>
</tr>
<tr>
<td>Poon 1999 [37]</td>
<td>230</td>
<td>250 µg/h x 12.5 h</td>
<td>9.9%*</td>
<td>2.8%*</td>
</tr>
<tr>
<td>Andruilli 2002 [39]</td>
<td>396</td>
<td>750 µg x 2.5 h</td>
<td>6.5%</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

*Significant difference between the control group and the somatostatin group; no significant differences in the other trials. AP: acute pancreatitis

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randomized trials involving a small number of patients demonstrated a trend towards reduced incidence of post-ERCP pancreatitis, but the differences were not statistically significant probably because of the small sample size [33, 34, 35]. However, in a study involving only 21 patients, Guelrud et al. [36] showed that infusion of somatostatin for 13 hours at a dose of 250 µg per hour significantly reduced the frequency of pancreatitis after balloon dilation of the pancreatic duct sphincter, which is a procedure associated with a high risk of post-ERCP pancreatitis. We conducted a randomized controlled trial involving 230 patients receiving an intravenous infusion of somatostatin at a dose of 250 µg per hour started 30 minutes before the ERCP procedure and continued for 12 hours after the procedure [37]. A significant decrease in the incidence of post-ERCP pancreatitis with the use of prophylactic somatostatin infusion (2.8%) as compared to the placebo group (9.9%) was noted. Of all the clinical trials on the use of prophylactic somatostatin to prevent post-ERCP pancreatitis published before the year 2000, a meta-analysis by Andruilli et al. [38] indicated that somatostatin reduces the risk of post-ERCP pancreatitis with an odds ratio of 0.38 as compared to the control groups in the trials. However, in a randomized controlled trial, the same group recently reported that infusion of somatostatin at a dose of 750 µg started 30 minutes before the procedure and continued for two hours did not reduce the incidence of post-ERCP pancreatitis as compared to the placebo group [39]. When the results of the latter trial were included into a meta-analysis, Andruilli et al. [39] found that the protective effect of somatostatin infusion fell short of being significant (odds ratio 0.68, P=0.075). The authors suggested that short-term infusion of somatostatin might not be effective in preventing post-ERCP pancreatitis. The discrepancies of the meta-analyses and the results of different randomized trials are probably due to the heterogeneity of the patients under study and the differences in experimental design.

Clinical Results of Octreotide as a Prophylactic Agent for Post-ERCP Pancreatitis

Octreotide is a longer acting analogue of somatostatin and has the advantage of simple administration by subcutaneous injection. In 1991, Tulassay et al. [40] reported that octreotide was effective in reducing the incidence of hyperamylasemia after ERCP from 44.1% in the control group (n=34) to 10.3% in 29 patients who received a single dose of 0.1 mg octreotide before the ERCP procedure. The incidence of acute pancreatitis was not assessed in that study. Subsequently, several studies have evaluated the effect of octreotide on the incidence of clinical pancreatitis after ERCP (Table 2).

In a multicenter randomized controlled trial involving 84 patients, Sternlieb et al. [41] found that treatment with octreotide significantly increased the incidence of post-ERCP pancreatitis as compared to the control group. Interestingly, octreotide appeared to

<table>
<thead>
<tr>
<th>Study</th>
<th>Total number of patients</th>
<th>Dosage regimen of octreotide</th>
<th>AP in control group</th>
<th>AP in treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sternlieb 1992 [41]</td>
<td>84</td>
<td>0.1 mg before and 45 min after</td>
<td>11%*</td>
<td>35%*</td>
</tr>
<tr>
<td>Binmoeller 1992 [42]</td>
<td>245</td>
<td>0.1 mg before and 45 min after</td>
<td>1.6%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Testoni 1994 [45]</td>
<td>40</td>
<td>0.1 mg 30 min before</td>
<td>0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Arcidiacono 1994 [43]</td>
<td>151</td>
<td>0.1 mg before and 4 h after</td>
<td>6.6%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Arvantidis 1998 [44]</td>
<td>73</td>
<td>4 µg/kg bolus</td>
<td>11.1%</td>
<td>10.8%</td>
</tr>
<tr>
<td>Testoni 2001 [47]</td>
<td>114</td>
<td>0.2 mg 24, 16, 8 and 0 h before</td>
<td>14.3%</td>
<td>12.0%</td>
</tr>
</tbody>
</table>

*Significant difference between the control group and the somatostatin group; no significant differences in the other trials

AP: acute pancreatitis
reduce the severity of pancreatitis in terms of number of days with pain, length of stay and the degree of amylase elevation, although pancreatitis was more common in the octreotide group. Nevertheless, the authors concluded that the use of octreotide before diagnostic or therapeutic ERCP could not be recommended. Subsequent randomized clinical studies by other authors have shown no significant difference in the incidence of post-ERCP pancreatitis between patients who received octreotide and those who received a placebo [42, 43, 44]. Testoni et al. [45] demonstrated a significantly reduced incidence of hyperamylasemia after endoscopic sphincterotomy in 20 patients treated with octreotide before the procedure as compared to another 20 patients who received a placebo. However, the study did not show a significant reduction in the incidence of clinical pancreatitis among patients treated with octreotide. In a latter randomized trial involving 60 patients, the same group demonstrated that a 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 [46]. However, this regimen of prolonged administration of octreotide is not practical. In a recent randomized trial reported by the same authors in the year 2001, 24-hour prophylaxis using octreotide before the procedure did not reduce the incidence of pancreatitis in selected patients at high risk for post-ERCP pancreatitis [47]. Similar to the findings of Sternlieb et al. [41], the study by Testoni et al. [47] suggested that octreotide might be of some advantage in reducing the severity of post-ERCP pancreatitis and length of stay, although the difference in these parameters between the octreotide group and the control group was not significant. In the meta-analysis of clinical trials before the year 2000 as reported by Andruilli et al. [38], octreotide was only associated with a reduced risk of post-ERCP hyperamylasemia but had no effect on acute pancreatitis and pain.

The exact reason for the different outcome of somatostatin and octreotide in the prophylaxis of post-ERCP pancreatitis remains unclear. One likely explanation might be that the octreotide increases basal pressure of the sphincter of Oddi [38]. However, in the recent trial by Testoni et al. [47], difficult cannulation of either Vater’s papilla or of the desired duct was more frequent in the control group than in the group treated with octreotide. This finding suggested that subcutaneous injection of octreotide at least one hour before the procedure does not affect the sphincter of Oddi contraction.

Discussion

The role of antisecretory agents in the prevention of post-ERCP pancreatitis remains controversial. The differences in results in the different studies are attributable to the different patient populations in terms of risk of post-ERCP pancreatitis and the wide variation in the dosage regimens used. The difficulty in the interpretation of the data is well-reflected by the different outcomes in the two meta-analyses performed by Andruilli et al. [38, 39], with one showing a definite benefit with the use of somatostatin but the other showing a non-significant trend of benefit after the addition of only one randomized study. The overall evidence in the literature does suggest 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 differential effects of the two agents on the motor function of sphincter of Oddi or to other reasons is unclear. The current data suggest that long-term infusion of somatostatin for 12 hours or more instead of short-term infusion for 2-4 hours is more likely to be beneficial in reducing post-ERCP pancreatitis. However, this may not be cost-effective, and the use of long-term continuous infusion is not suitable for outpatient ERCP procedures. The use of a single-dose bolus intravenous injection of
somatostatin is the most appealing approach in terms of cost-effectiveness and practicability in the outpatient setting. Data from Bordas et al. [32] on this simple approach are encouraging, but further randomized studies on the use of single-dose bolus intravenous injection of somatostatin as a prophylactic therapy for post-ERCP pancreatitis are needed to clarify its benefit. Since post-ERCP pancreatitis is usually mild and, in most cases, only results in prolonged hospital stay, [32, 37, 47] it is particularly important to evaluate the cost-effectiveness of the use of somatostatin as a prophylactic therapy. Unfortunately, this has not been evaluated in the clinical trials reported thus far. In the meta-analysis by Andruilli et al. [38] which demonstrated a significant benefit of prophylactic somatostatin, it was estimated that the number of patients who needed to be treated with somatostatin to prevent one single episode of acute pancreatitis was 13. Hence, it may not be cost-effective to administer somatostatin in all patients undergoing ERCP. It is obviously a more cost-effective approach to reserve the use of somatostatin to high-risk patients. In fact, studies have demonstrated that the benefit of somatostatin is more obvious in patients at high risk of pancreatitis, such as those with pancreatic duct sphincter manipulation and those with endoscopic sphincterotomy [32, 36]. However, most of the risk factors for post-ERCP pancreatitis are related to technical factors that will become obvious only during the procedure, thus making selective use of pre-procedure prophylactic somatostatin difficult in high-risk patients. Typically, a delay of a few hours exists between the pancreatic injury during ERCP and the peak of hyperamylasemia or onset of symptoms in post-ERCP pancreatitis [48]. Theoretically, this may provide a “therapeutic window” for drugs given after the initiation of pancreatic injury to work. It is worthwhile investigating the possible role of somatostatin or other prophylactic agents given immediately after the ERCP procedure. Finally, it is imperative to continue research to elucidate the best dosage regimen of somatostatin for the prophylaxis of post-ERCP pancreatitis and to compare its efficacy and cost-effectiveness with other agents such as protease inhibitors in the prevention of post-ERCP pancreatitis.

**Keywords**
Cholangiopancreatography, Endoscopic Retrograde; Endoscopic Sphincterotomy; Octreotide; Somatostatin

**Declaration of interest**
The authors do not have any financial interest involved in the drugs mentioned in the article

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