Somatostatin and somatostatin analogues – are they indicated in the management of acute pancreatitis?

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Abstract
Somatostatin was first suggested for the treatment of acute pancreatitis more than 15 years ago but despite many studies, its role in the management of this condition remains unclear. The experimental and clinical studies are reviewed and the physiological actions of somatostatin, which may influence the course of acute pancreatitis are examined. It is concluded that although some reports suggest a trend towards improved survival and lessened complication rate with somatostatin treatment, insufficient evidence of benefit exists to support the use of somatostatin or its analogue in the treatment or prophylaxis against acute pancreatitis in routine clinical practice.

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Somatostatin, a 14 amino acid peptide was discovered more than 20 years ago in the rat hypothalamus. Since then it has been identified in species from protozoa to humans and in a wide range of mammalian tissues. As our knowledge of its physiological role expands, so the list of conditions for which it is of potential therapeutic benefit grows longer.

In addition to its use in the management of acromegaly, somatostatin or its analogue, octreotide (SMS 201–995, Sandostatin), has been used in the treatment of acute pancreatitis, pancreatic and enterocutaneous fistulas, pancreatic pseudocysts, varical haemorrhage, secretory diarrhoeas, and the short bowel syndrome. It has also been used successfully in the palliation of some endocrine tumours, most notably carcinoid. The use of somatostatin in acute pancreatitis was first suggested in 1975 but despite much experimental and clinical study since that time, its role in the management of this condition remains unclear.

Physiological effects of somatostatin
There are four properties of somatostatin in pharmacological doses which may influence the course of acute pancreatitis.

INHIBITION OF Pancreatic secretion
It is conventional wisdom that ‘to rest the gland’ is beneficial in the management of acute pancreatitis. Although the validity of this assumption has not been established it has led to clinical trials with nasogastric suction, cimetidine, and glucagon in the treatment of acute pancreatitis, none of which has been shown to be effective.

Somatostatin causes a dose dependent reduction in exocrine pancreatic secretion, the effect on enzyme secretion being greater than the effect on secretion of bicarbonate and water. Similar effects have been shown with the somatostatin analogue, octreotide. In health, the doses of somatostatin used in clinical trials would be expected to cause a 70% reduction in exocrine pancreatic secretion. This may explain the successful use of somatostatin analogues in the treatment of pancreatic fistulas and pseudocysts. The secretory state of the pancreas, however, in acute pancreatitis is unknown, as is the effect of somatostatin on the diseased gland. In experimental models at least, pancreaticsecretion seems to remain at basal values and there is evidence that pancreatic exocrine secretion is impaired in most patients after recovery from necrotising pancreatitis.

HAEMODYNAMIC EFFECTS
Somatostatin reduces pancreatic blood flow in experimental animals. The development of pancreatic necrosis has been linked to hypoperfusion of the gland and vasoconstrictors have been shown to worsen the histological severity of experimental pancreatitis. Conversely, dopamine, which improves pancreatic blood flow, has been found to improve the outcome from experimental pancreatitis.

Schroeder et al found that, after the induction of pancreatitis, pancreatic blood flow decreased to a greater extent in somatostatin treated piglets than in untreated controls. This would be expected to be associated with a deleterious effect on outcome although no difference between treated and untreated animals was seen in this study.

CYTOPROTECTION/ORGANOPROTECTION
Cytoprotective properties have been claimed for somatostatin on the basis of its ability to reduce the effect of various toxins on gastric mucosal cells and hepatocytes. Cytoprotection towards the pancreas, however, has not been proved and experiments have shown that, for somatostatin to be effective in this context, pretreatment is necessary. Obviously in acute pancreatitis, where organ damage will have occurred before admission, such pretreatment would not be possible.

STIMULATION OF THE RETICULOENDOTHELIAL SYSTEM
The fourth way in which somatostatin may influence the course of acute pancreatitis is by its stimulatory effect on the phagocytic cells of the reticuloendothelial system. In experimental
Somatostatin in the treatment of experimental acute pancreatitis

<table>
<thead>
<tr>
<th>Author</th>
<th>Model</th>
<th>Survival benefit</th>
<th>Histological benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lankisch et al.</td>
<td>Rat, bile injection</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Schwedes et al.</td>
<td>Dog, bile injection</td>
<td>N/A</td>
<td>Yes</td>
</tr>
<tr>
<td>Adler et al.</td>
<td>Rat, secretagogue</td>
<td>N/A</td>
<td>Yes</td>
</tr>
<tr>
<td>Baxter et al.</td>
<td>Rat, duct ligation</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Degertekin et al.</td>
<td>Mouse, diet</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Schlarman et al.</td>
<td>Dog, bile injection</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td>De Rai et al.</td>
<td>Rat, duodenal loop</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

N/A = not assessed; bile injection = retrograde injection of bile or bile salts into the pancreatic duct; secretagogue = intravenous administration of cerulein; duct ligation = formation of a common bile/pancreatic duct.

acute pancreatitis, survival can be improved by stimulation of the reticuloendothelial system with either zymosan or glucan.\(^{11,12}\) Conversely, depression of the reticuloendothelial system results in worsened survival.\(^{12}\) There is also some evidence of reticuloendothelial system depression in patients with acute pancreatitis.\(^{13}\)

Both somatostatin and the longacting somatostatin analogue, octreotide, have been shown to increase the clearance of colloidal carbon.\(^{14,15}\) Somatostatin was found to be more effective in this regard than Zymosan.\(^{16}\) Somatostatin has also been reported to enhance monocyte phagocytic activity in vitro.\(^{17}\) Survival of rats after intraperitoneal injection of endotoxin was also improved with somatostatin treatment,\(^{18}\) which may have been a consequence of reticuloendothelial system stimulation.

SERUM SOMATOSTATIN IN EXPERIMENTAL PANCREATITIS

Somatostatin has been examined in most animal models of acute pancreatitis and has met with varying degrees of success (Table I). In the first study to be reported,\(^{19}\) Lankisch et al. gave somatostatin at a dose of 100 \(\mu g/100\) g body weight for three hours immediately after inducing pancreatitis in rats by the retrograde injection of sodium taurocholate into the pancreatic duct. Although the serum amylase and lipase were lower in the treatment group, the overall mortality was unchanged. The histological changes in the pancreas were also similar in the two groups. Two years later, Schwedes et al.\(^{16}\) reported a significant histological benefit with cyclic somatostatin, 62-5 \(\mu g/h\) in a canine model of haemorrhagic pancreatitis. This effect was seen with both somatostatin pretreatment and with somatostatin given two hours after the induction of pancreatitis. The general condition of the animals in the treated group was also noted to be improved.

In addition to the different species used in these experiments, there are differences in experimental design which may help to explain these contradictory results. In inducing acute pancreatitis, Lankisch et al. used sodium taurocholate whereas Schwedes et al. used the animals own bile. Neither group of workers standardized the injection pressures used, a factor which may influence the severity of pancreatitis produced. There was also a difference in the length of somatostatin treatment between the two studies. Whereas Lankisch et al. stopped treatment after three hours, Schwedes et al. gave somatostatin by continuous infusion for up to 24 hours. Native somatostatin has a half life in the circulation of only two to three minutes\(^{19}\) and it is possible that prolonged treatment in the second study was responsible for the difference in result.

Subsequently, Schlarman et al.\(^{13}\) reported no improvement in pancreatic histology after the infusion of native somatostatin 20 \(\mu g/kg/h\) for five hours immediately after the induction of pancreatitis by retrograde bile injection in dogs, although portal and thoracic duct lymph amylase activities were reduced in the treatment group. Similarly, Degertekin et al.\(^{11}\) using a diet induced model of acute pancreatitis in mice, failed to show a significant effect on survival or pancreatic histology after the subcutaneous administration of native somatostatin, 30 \(\mu g\) every eight hours. In view of the short circulation half life of somatostatin,\(^{17}\) however, it is unlikely that such a dose schedule would achieve therapeutic values in plasma. It is therefore difficult to draw firm conclusions from this study.

A beneficial effect of cyclic somatostatin, 5 \(\mu g/kg/h\), on the histological severity of cerulein induced pancreatitis was reported by Adler et al.\(^{14}\) This effect was observed immediately after the induction of pancreatitis. Similarly, De Rai et al.\(^{20}\) showed reduced histological damage with somatostatin given intravenously for nine hours. No information on the timing or dose of treatment was given. Baxter et al.\(^{18}\) in addition to showing a histological benefit with somatostatin treatment, found a dramatic improvement in survival in the treatment group. They continued somatostatin, 4 \(\mu g/kg/h\) body weight, for up to 24 hours using a duct ligation model in the rat. Similar results were seen even if treatment was started immediately or delayed for 24 hours after duct ligation. These results suggest that differences in duration of treatment, but not in timing of treatment or size of dose, may explain some of the differences in results obtained.

Differences between the experimental models used may also play a part in the contradictory results. In the only study to show a survival difference, Baxter et al. induced acute pancreatitis in rats by ligation of the common bile/pancreatic duct. This model is normally associated with pancreatic oedema\(^{19}\) although pancreatic necrosis and a high mortality were seen in the control group in this study.

The development of the longacting somatostatin analogue, octreotide, has led to its use in experimental pancreatitis. Its longer half life allows subcutaneous administration avoiding the need for continuous intravenous infusion. The four experimental studies reported to date all show some benefit from octreotide administration (Table II).

In the one study to assess survival,\(^{18}\) a dramatic advantage was seen after twice daily subcutaneous octreotide at a dose of 2 \(\mu g/kg\) starting 12 hours after the induction of pancreatitis by pancreatic duct ligation. This survival advantage was similar to that reported by the same authors using native somatostatin. Augelli et al.\(^{20}\) were able to show a reduction in histological severity in animals given octreotide, 5 \(\mu g/h\), before the induction of pancreatitis although no effect was seen if treatment was delayed until pancreatitis was established despite continuing treatment for...
24 hours. Similarly, Zhu et al.\textsuperscript{41} giving octreotide 2 \( \mu g/kg \) for 4 days showed a reduction in histological severity in a rat bile injection model. Once again, this effect was only seen if treatment was commenced before the induction of pancreatitis.

In the study by Davliakos et al.\textsuperscript{42} an ex vivo model was used and histological benefit was seen after only one injection of octreotide, even if treatment was delayed until one hour after the induction of pancreatitis. Ex vivo models, however, have been criticised as being unphysiological\textsuperscript{43-45} and their usefulness in evaluating treatment effects remains to be established.

In summary, the evidence from experimental studies is inconclusive although in those studies that continue treatment over a prolonged period, there is evidence of some improvement in the treatment group. Differences between studies are not explained by the size of dose or the timing of administration in relation to the induction of pancreatitis. Only one study to date has reported an overall reduction in mortality with somatostatin.

### Clinical trials with somatostatin in acute pancreatitis

The main difficulty in therapeutic trials in acute pancreatitis is that only a very small proportion of those with the disease are likely to benefit significantly from specific treatment and it is therefore necessary to recruit large numbers of patients to be confident of showing a reduction in mortality. As with other proposed treatments in acute pancreatitis, clinical trials with somatostatin have often failed to recruit sufficient patients for meaningful conclusions to be drawn.

After small, uncontrolled reports in the late 1970s suggesting clinical improvement with somatostatin in acute pancreatitis a multicentre study was carried out.\textsuperscript{17} The APTS study (Acute Pancreatitis Treatment with Somatostatin)\textsuperscript{17} was conducted between centres in Germany, Switzerland, and Greece and was intended to include only patients with severe disease. Severe acute pancreatitis was defined as hyperamylasaemia and abdominal pain with three or more of five severity criteria present: shock, ileus, abdominal distension, white cell count greater than 12 000 cells/dl, and glucose greater than 150 mg/dl. Somatostatin 250 \( \mu g/h \) or placebo was infused for up to seven days. A total of 77 patients were recruited over a two year period, 36 in the treatment group and 41 in the control group. The authors of the multicentre study reported that six deaths in the control group (17\%) and four in the treatment group (11\%) a difference that fails to reach statistical significance. This led the authors to conclude that somatostatin was of no benefit in acute pancreatitis. It is important to realise, however, that this study has insufficient numbers of patients to exclude a survival advantage as large as 50\%. It can be readily calculated from sample size nomograms that more than 200 patients would be required in each group to exclude a type II error where the death in the control group is only 17\%,\textsuperscript{29}

The authors found that serum pancreatic enzyme concentrations returned to normal more quickly in the treatment group, but unfortunately no detailed analysis was made of the incidence of complications in the two groups, perhaps reflecting difficulties in collating this information in a multicentre study.

Since 1985 there have been a further three controlled clinical trials reported in English language publications, all of which recruited patients with both mild and severe acute pancreatitis.

Choi et al. in Hong Kong\textsuperscript{46} conducted a randomised controlled trial comparing somatostatin with standard treatment in patients with acute pancreatitis. Only 71 patients were recruited of whom 15 had prognostically severe disease based on the presence of three or more positive Glasgow criteria.

Patients were randomised on admission to standard treatment and somatostatin 100 \( \mu g/h \) for two days by continuous intravenous infusion or to standard treatment alone. With such small numbers of patients, it is impossible to assess any effect on mortality alone and indeed there were only three deaths overall, two in the control group and one in the treatment group. There was a statistically significant difference in the complication rate between the two groups, which was mainly accounted for by local complications, in particular 'pancreatic phlegmon', which the authors defined as inflammatory pancreatic swelling seen by computed tomography with associated fluid collection.

A multicentre study was reported by D'Amico et al.\textsuperscript{47} in which a total of 164 patients were recruited over a two year period. Patients with acute pancreatitis of every grade of severity were included resulting in an overall mortality of 5.5\%. No information was given about the randomisation procedure. Somewhat unusually, patients were divided into those requiring immediate surgery and those needing medical treatment alone based on a clinical and radiological assessment of disease severity. Patients not having immediate surgery were then given either total parenteral nutrition alone or total parenteral nutrition with somatostatin, 250 \( \mu g/h \) for five days. Patients who subsequently worsened and required surgery were excluded from the study. There was a further subdivision of patients into 'haemorrhagic' and 'oedematous' pancreatitis based upon the operative findings and clinical course. Overall, there was a trend towards a reduction in death in the somatostatin treated group, which failed to reach statistical significance (2 vs 7). Again, there were less local complications in the treatment group compared with the control group (1 vs 5) although observer bias cannot be excluded and the numbers are too small to allow meaningful statistical analysis. The authors concluded that surgery was reduced in the somatostatin treat-
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TABLE III  Somatostatin and octreotide in the prophylaxis against ERCP induced pancreatitis

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Drug</th>
<th>Effect</th>
</tr>
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<tbody>
<tr>
<td>Tulassay et al</td>
<td>63</td>
<td>Octreotide</td>
<td>Less enzyme rise pain</td>
</tr>
<tr>
<td>Cicero et al</td>
<td>38</td>
<td>Somatostatin</td>
<td>Less enzyme rise pain</td>
</tr>
<tr>
<td>Bordas et al</td>
<td>33</td>
<td>Somatostatin</td>
<td>Less enzyme rise pain</td>
</tr>
<tr>
<td>Guelrud et al</td>
<td>16</td>
<td>Somatostatin</td>
<td>Less pancreatitis</td>
</tr>
<tr>
<td>Sarti et al</td>
<td>56</td>
<td>Somatostatin</td>
<td>None</td>
</tr>
<tr>
<td>Borsch et al</td>
<td>20</td>
<td>Somatostatin</td>
<td>None</td>
</tr>
<tr>
<td>Testoni et al</td>
<td>54</td>
<td>Somatostatin</td>
<td>None</td>
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<tr>
<td>Sterneleb et al</td>
<td>84</td>
<td>Octreotide</td>
<td>More pancreatitis</td>
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<tr>
<td>Binmoeller et al</td>
<td>245</td>
<td>Octreotide</td>
<td>None</td>
</tr>
</tbody>
</table>

found an overall incidence of acute pancreatitis of 43%. Infusion of somatostatin for 12 hours peroperatively resulted in an incidence of acute pancreatitis of 25% compared with 75% in the placebo group. Another study, however, has reported a significant increase in the incidence of acute pancreatitis from 11% to 34% after the prophylactic use of octreotide, suggesting that the use of octreotide may even be harmful.

In conclusion, it is the authors' opinion that the evidence currently available does not support the use of somatostatin or its analogue for the treatment or prophylaxis against acute pancreatitis in routine clinical practice.

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