

Efficacy of somatostatin in acute pancreatitis

Baldea Corina, Popovici Raluca

University of Oradea – Faculty of Environmental Protection , Gen Magheru, nr. 26

Abstract

Interest in the use of somatostatin in the treatment of acute pancreatitis began in the mid 1970s when it was first demonstrated to inhibit pancreatic secretion. Somatostatin relaxes the sphincter of Oddi, allowing free drainage of any pancreatic secretion into the duodenum. Somatostatin reduced pancreatic blood flow in piglets, but no difference in outcome was observed between treated and untreated animals.

Somatostatin prevent the early hyperaemia associated with inflammation in early experimental acute pancreatitis but maintain perfusion in the latter stages when necrosis is present.

Key words: somatostatin, endotoxaemia, Kupffer cells, enzymes

INTRODUCTION

Interest in the use of somatostatin in the treatment of acute pancreatitis began in the mid 1970s when it was first demonstrated to inhibit pancreatic secretion. Subsequently, in the early 1980s somatostatin and its analogue were demonstrated to ameliorate established acute pancreatitis and to improve survival in experimental animals. Although a beneficial, or no effect, of somatostatin in experimental acute pancreatitis has been repeatedly demonstrated, the analogue has been shown to have a detrimental effect in caerulein induced pancreatitis in mice. The early beneficial effect of somatostatin in experimentally induced acute pancreatitis led to the suggestion that it may be of value in the management of this serious and potentially life-threatening condition in man.

Mechanism of action:

Inhibition of pancreatic secretion

Acute pancreatitis is characterised by autodigestion of the gland by activated digestive enzymes.

Numerous studies indicate that somatostatin are potent inhibitor of pancreatic enzyme secretion, and it was proposed initially that their beneficial effects in acute pancreatitis were mediated by this mechanism.

The reticuloendothelial system and endotoxaemia

Endotoxaemia is common in severe acute pancreatitis as a result of translocation of bacteria and endotoxins across the wall of the gastrointestinal tract. Normally, the endotoxins which arrive in the portal blood from the intestine are removed by the Kupffer cells in the liver; these comprise the hepatic component of the reticuloendothelial system (RES). In experimental animals and humans hepatic RES activity is decreased during acute pancreatitis. This may be responsible for the accompanying systemic endotoxaemia, a suggestion supported by observation that somatostatin are potent stimulators of hepatic RES activity, reduce the degree of systemic endotoxaemia and improve pulmonary function in rats with acute pancreatitis.

Cytoprotection

Cytoprotective effects have been claimed for somatostatin, reduce the effects of toxins on gastric mucosal cells, hepatocytes, and rat pancreatic cells. The mechanism whereby somatostatin exert this cytoprotective effect with respect to the pancreas is unknown but may be via modulation of the cytokine cascade and prostaglandin production.

Motility of the sphincter of Oddi

Somatostatin relaxes the sphincter of Oddi, allowing free drainage of any pancreatic secretion into the duodenum. This relieves any ductular hypertension and protects the acinar cells from the digestive action of any activated enzymes. However, it could be detrimental in acute pancreatitis since it may result in the reflux of duodenal juices containing activated enzymes.

Haemodynamic effects

In contrast to the possible benefits of somatostatin discussed above, it has been suggested that their effects on pancreatic blood flow could be detrimental in acute pancreatitis. Hypoperfusion of the pancreas has been linked to pancreatic necrosis, and vasoconstrictors have worsened the histological severity of experimental pancreatitis.

Somatostatin reduced pancreatic blood flow in piglets, but no difference in outcome was observed between treated and untreated animals.

Somatostatin prevent the early hyperaemia associated with inflammation in early experimental acute pancreatitis but maintain perfusion in the latter stages when necrosis is present.

MATERIAL AND METHOD

A trial was organised in order to establish the role of somatostatin in the treatment of acute pancreatitis. In this trial 77 patients were included and randomized in two groups. The first one received supportive therapy alone, and the second received also a 7-day infusion of somatostatin.

III. Results and conclusion

Although interest in the use of somatostatin in acute pancreatitis began in 1980, it is only recently that its therapeutic value in this potentially life-threatening disease is becoming established. The main difficulty in establishing the role of somatostatin in acute pancreatitis has been the failure of many trials to take into account the natural history of the disease.

Approximately 80% of patients present with mild, self-limiting acute interstitial pancreatitis which resolves spontaneously without specific therapy. However, approximately 20% of patients with acute pancreatitis will develop a severe form of the disease characterised by peri-pancreatic and intrapancreatic necrosis. This is associated with a mortality in excess of 20% and which, in some series, approaches 60%.

The first evaluation of the efficacy of somatostatin in the treatment of acute pancreatitis was in Germany. In this multicentre trial, the inclusion criteria included amylase levels three times higher than normal, abdominal pain for more than 48 hours, ileus, abdominal distension, shock, leucocytosis, hyperglycaemia and necrotising pancreatitis at operation. However, some of these criteria, namely increased serum amylase levels, abdominal pain, ileus and distension are not considered prognostic for severe acute pancreatitis. It was anticipated that between 200 to 300 patients would be required in each arm to show a significant benefit of somatostatin on hospital mortality, the main endpoint of the trial. Patients were randomised to receive supportive therapy alone or in combination with a 7-day infusion of somatostatin. The trial was closed prematurely in 1985 after only 77 patients had been entered and randomised to somatostatin or supportive therapy.

The mortality in the somatostatin group (11%) was less than in the control group (17%), but the difference did not reach statistical significance. Conclusion it was that somatostatin was of no benefit in the treatment of severe acute pancreatitis. This conclusion is not valid, however, since there were a number of deficiencies in the trial. The overall mortality rate (14%) is lower than would be expected if only patients with severe acute

pancreatitis had been included in the trial. Clearly, some patients with mild interstitial acute pancreatitis had been randomised to receive somatostatin or supportive therapy, and it would be important to know the distribution of these patients with mild acute pancreatitis was uniform between the two groups, the number of patients included in the study would be insufficient to exclude a survival advantage of somatostatin as great as 50%. Furthermore, if the trend in mortality from 17 to 11% observed in the first 77 patients were to be maintained for 500 patients, the results would have been significantly in favour of somatostatin therapy, with a defined probability error of 5% and 95% confidence intervals.

Beneficial effects of somatostatin in severe acute pancreatitis.

Improvement with somatostatin was calculated by expressing the difference between the two groups as a percentage of the complication rate in the control group.

Tab.nr.1

| Complication | Somatostatin | Control | %Improvement with somatostatin |
|---------------------------|--------------|---------|--------------------------------|
| Shok | 40% | 41% | 3% |
| Respiratory insufficiency | 6% | 14% | 60% |
| Renal insufficiency | 5% | 14% | 67% |
| Sepsis | 2% | 7% | 79% |
| Bleeding | 6% | 4% | 56% |
| Mortality | 19% | 24% | 20% |

Efficacy of somatostatin in severe acute pancreatitis

Tab.nr.2

| | Control | Somatostatin |
|-----------------------------|---------|--------------|
| Complication-mortality rate | 60% | 80% |
| Mortality | 40% | 20% |

CONCLUSIONS

1. Numerous studies indicate that somatostatin are potent inhibitor of pancreatic enzyme secretion, and it was proposed initially that their beneficial effects in acute pancreatitis were mediated by this mechanism.
2. Endotoxaemia is common in severe acute pancreatitis as a result of translocation of bacteria and endotoxins across the wall of the gastrointestinal tract.
3. Cytoprotective effects have been claimed for somatostatin, reduce the effects of toxins on gastric mucosal cells, hepatocytes, and rat pancreatic cells.
4. Somatostatin relaxes the sphincter of Oddi, allowing free drainage of any pancreatic secretion into the duodenum.
5. Somatostatin reduced pancreatic blood flow in piglets, but no difference in outcome was observed between treated and untreated animals.
6. Somatostatin prevent the early hyperaemia associated with inflammation in early experimental acute pancreatitis but maintain perfusion in the latter stages when necrosis is present.

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