Leading article

Therapeutic potential of a long acting somatostatin analogue in gastrointestinal diseases

Somatostatin, a naturally occurring peptide (Figure), was first discovered more than 20 years ago. The gastrointestinal tract and pancreas contain more somatostatin than any other organ. When infused intravenously the hormone modulates numerous gut functions although its exact physiological and biological role are still not fully defined. Administration of somatostatin reduces gastric acid and pancreatic secretion, small gut transit, absorption of intestinal nutrients and gastrointestinal blood flow. Gastric emptying is enhanced at low plasma somatostatin concentrations and inhibited at high concentrations. The therapeutic application of somatostatin has been limited by its short circulating half-life of about two minutes and the need for parenteral administration. The development of a long acting cyclic octapeptide somatostatin analogue (SMS 201–995, octreotide) (Figure) with a circulating half-life of one to two hours after subcutaneous administration, has therapeutic potential. It could be of value in gastrointestinal bleeding, intestinal fistulae, the short bowel syndrome, pancreatitis, the dumping syndrome and gut related endocrine tumours.

Gastrointestinal bleeding

Control of variceal bleeding may be the area of greatest clinical impact. Somatostatin reduces portal pressure, hepatic blood flow and azygous

![Amino acid sequence of native somatostatin-14 and octreotide.](image)
blood flow in patients with cirrhosis but reports claiming that it reduces intravariceal pressure have not been confirmed. Somatostatin infusion has no appreciable effect on systemic haemodynamics although with bolus injections of either somatostatin or octreotide there may be transient reductions in heart rate and cardiac output and a rise in mean arterial blood pressure.

Two controlled clinical trials comparing somatostatin infusion with vasopressin infusion for bleeding oesophageal varices have been reported. Kravetz et al reported that somatostatin infusion (50 µg bolus and 250 µg/h) stopped bleeding in 87% of patients for up to three hours after starting treatment and was as effective as vasopressin for up to 48 h. Jenkins et al found that somatostatin infusion of similar concentrations controlled variceal haemorrhage during the first 18–24 h in all 10 patients compared with four of 12 treated with vasopressin infusion (p=0.003). In both studies major and minor complications of treatment were less with somatostatin than with vasopressin. Comparison of somatostatin with combined vasopressin and glyceryl trinitrate has not been reported.

McKee et al have compared variceal tamponade and octreotide infusion (25 µg/h) in patients with acute variceal bleeding. Bleeding control was similar in both groups at four and 48 h after the start of treatment. Five deaths occurred in the 20 patients treated with variceal tamponade whereas all 20 patients treated with octreotide survived (p<0.047). In a similar study somatostatin infusion proved superior to variceal tamponade in controlling haemorrhage and produced fewer complications.

Thus, octreotide is an effective treatment for the management of acute variceal bleeding, controlling approximately 90% of bleeding episodes in the first four hours. Its lack of side effects, ease of administration and patient acceptability should ensure that it becomes the treatment of choice for the initial management of variceal haemorrhage before definitive treatment with sclerotherapy or oesophageal transection. If subcutaneous administration of octreotide is as effective as infusion, the drug could make a useful contribution to early, pre hospital management of bleeding varices.

Somatostatin infusion reduces gastric and splanchnic blood flow. Three controlled studies with small numbers of patients indicated that somatostatin infusion was superior to placebo and H2-receptor antagonists in controlling bleeding from peptic ulcers. In a large placebo controlled study with over 300 patients, somatostatin infusion in each arm showed no benefit when compared with placebo in the treatment of acute haematemesis and melaena. In a condition where there is a 70–80% spontaneous cure rate, drug therapy has to be either extremely effective or directed towards those most likely to have persistent bleeding. Somatostatin and octreotide could be of benefit in a highly selected group of patients with gastrointestinal bleeding who are at high risk of rebleeding as defined by clinical and endoscopic criteria.

**Fistulae and the short bowel syndrome**

In several open trials, relatively high doses of either somatostatin infusion or eight hourly subcutaneous octreotide close nearly 80% of enterocutaneous fistulae within an average of four to five days. One group have reported much poorer results. Somatostatin or octreotide was given in addition to
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conventional treatment with total parenteral nutrition (TPN). Somatostatin and octreotide were least effective in the presence of continuing infection or inflammatory activity, cancer or distal intestinal obstruction. There has been no report of a controlled trial with octreotide in the management of enterocutaneous fistulae so that it is uncertain whether the administration of octreotide with TPN is significantly superior to TPN alone.

Open trials of both somatostatin infusion and octreotide 0·1 mg to 0·6 mg per day report accelerated closure of approximately 50–80% of pancreatic fistulae occurring after pancreatitis, subtotal pancreatectomy or surgical trauma. Pancreatic duct obstruction, malignancy, or unresolved sepsis should be excluded before starting octreotide.

Octreotide increased water, sodium and calorie absorption in patients with the short bowel syndrome dependent on longterm TPN or parenteral fluid and electrolyte supplementation. This reduced the daily requirements of parenteral supplementation and was discontinued completely in one patient.

Pancreatitis

Both somatostatin and octreotide prevent the occurrence and reduce the severity of bile induced pancreatitis in an experimental animal model. Octreotide did not confer benefit in animals with diet induced pancreatitis.

In open trials in humans somatostatin infusion appeared beneficial in the treatment of acute pancreatitis but controlled trials although showing a favourable trend have failed to show a clearcut benefit. Future trials will need larger numbers of patients, including those with severe pancreatitis and should incorporate a severity based stratification before randomisation.

Somatostatin infusion may reduce pain, pancreatic swelling and hyperamylasaemia after ERCP but as severe pancreatitis only occurs in a few patients, it is premature to advocate the routine prophylactic use of octreotide during this procedure.

Irritable bowel syndrome

An intriguing case report described relief of irritable bowel syndrome (IBS) symptoms in a patient receiving subcutaneous somatostatin for acromegaly. The history of irritable bowel predated that of the acromegaly. The patient had received numerous previous treatments for IBS and acromegaly, none of which had produced relief of her symptoms, so a placebo effect was thought unlikely. It was suggested that a deficiency of somatostatin may be involved in the pathogenesis of IBS.

There is a trend towards reduced fasting and peak postprandial plasma concentrations of somatostatin in patients with ‘diarrhoea’ predominant IBS. The pathogenetic significance of this finding remains obscure but therapeutic use of octreotide in the IBS is a tantalising possibility.

Dumping syndrome

Octreotide and somatostatin have been used in the treatment of the dumping syndrome because of their effects on gastric emptying, intestinal
secretion and glucose tolerance. With dumping provocation tests both somatostatin and octreotide abolish or reduce early and late dumping symptoms associated with hypovolaemia and hypoglycaemia, respectively.\textsuperscript{55,60} Although in the long-term some patients receive benefit from octreotide many others are unable to tolerate the drug because of the occurrence of diarrhoea.\textsuperscript{60,61} Paradoxical hypoglycaemia has been reported in patients with dumping syndrome after starting octreotide therapy due to suppression of glucagon as well as insulin secretion.

**Gut related endocrine tumours**

Somatostatin and octreotide have been used to treat digestive tract associated endocrine tumours such as VIPomas, carcinoid tumours, gastrinomas, insulinomas and glucagonomas. The clinical manifestations of these slow growing neoplasms are due to mass effects of the tumours and metastases and to secretion of biologically active hormones. If the tumours are resectable, surgery is indicated. Chemotherapy with streptozotocin and 5-fluouracil is not only toxic but also has a low tumour response rate.

There have been sporadic individual reports of tumour regression in man\textsuperscript{63-64} and in experimental animals\textsuperscript{65-66} but as yet there is no convincing evidence to indicate that octreotide produces clinically important tumour shrinkage. Nevertheless octreotide has produced dramatic symptomatic benefit for many patients by suppressing hormone secretion. Patients with VIPomas and torrential life threatening diarrhoea have had complete remission of their symptoms with octreotide and have been maintained long-term on twice daily subcutaneous injections without complications.\textsuperscript{67,68}

High doses of subcutaneous octreotide up to 250 μg three times a day can be effective in relieving symptoms of the carcinoid syndrome.\textsuperscript{69,70} Low doses produce little or no benefit.\textsuperscript{71-73} Although producing symptom relief, the effect of octreotide on 5-HIAA secretion from these tumours is variable suggesting that peripheral actions are important in the therapeutic effect.\textsuperscript{70} Somatostatin has been used in patients with carcinoid tumours to prevent perioperative hypotension.\textsuperscript{74}

In patients with gastrinomas a single subcutaneous injection of octreotide can suppress gastrin secretion for up to 18 h.\textsuperscript{75} Longterm symptomatic improvement in patients with the Zollinger-Ellison syndrome has also been described\textsuperscript{76} but with the advent of omeprazole there is a limited role for octreotide. Benefit from octreotide has been reported in patients with insulinomas\textsuperscript{77,78} and glucagonomas\textsuperscript{79,80} although this response is not as clearcut as with other tumours.\textsuperscript{81,82}

In the longterm management of these endocrine tumours, drug associated side effects are uncommon. Pain at the site of octreotide injection is frequent but generally acceptable. Biochemical glucose intolerance rarely progresses to overt diabetes. Steatorrhoea may occur with high doses. Rebound hypersecretion of tumour hormone may occur with drastic sequelae if octreotide therapy is discontinued\textsuperscript{83,84} and paradoxical hypoglycaemia has been described on starting therapy in patients with insulinomas.\textsuperscript{85}

**Conclusion**

Octreotide has been used therapeutically in a wide spectrum of gastro-
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intestinal conditions but further work is required before the exact indications for its use are fully defined. It may be of value in patients with bleeding oesophageal varices, enterocutaneous fistulae and gut related endocrine tumours. The possibility that octreotide may benefit irritable bowel patients requires further exploration. The development of an orally active somatostatin analogue is underway and is likely to be of great value.

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