Somatostatin analogue SMS 201–995 long term therapy for vipoma

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Introduction

The clinical picture of a pancreatic tumour secreting vasoactive intestinal polypeptide (VIPoma) is dominated by diarrhoea, and associated with hypokalaemia, hypochlorhydra, and alkalosis. An excess of vasoactive intestinal peptide (VIP) stimulates water secretion in the intestine and pancreas leading to a secretory diarrhoea which may be life threatening. The definitive treatment for a VIPoma is surgical removal, but presentation may occur after the tumour has metastasized or when major surgery is contraindicated by the patient’s general condition. Symptomatic treatment can be achieved with streptozotocin but this may have unpleasant side effects. We describe an elderly patient with a pancreatic VIPoma who has been treated symptomatically with a somatostatin analogue for 24 months.

Case report

In May 1984 a 79 year old retired salesman was referred with a seven month history of profuse, dark, watery, explosive diarrhoea, and burning sensation in the rectum on defaecation. Despite a good appetite he had lost 2 stones in weight. On examination he was clinically anaemic and had obvious weight loss. There were signs of congestive heart failure. Abdominal examination revealed an ill-defined, irregular, non-tender mass in the epigastrium.

Initial investigations revealed a hypokalaemic alkalosis (potassium 3.2 mmol/l, bicarbonate 30 mmol/l) with normal urea and liver function tests. The haemoglobin was 4.2 g/dl with an iron deficiency picture. He was carefully transfused with 4 units of blood and the signs of cardiac failure resolved.

Barium studies demonstrated a mass displacing the duodenum. Abdominal ultrasound showed this to be a large mass causing separation of the aorta and inferior vena cava arising from the uncinate process of the pancreas. There were no hepatic metastases. Endoscopic retrograde cholangiopancreatography (ERCP) showed a mass in the head of the pancreas with compression of the pancreatic duct. A small gastric ulcer was seen high on the lesser curve with an ulcer in the second part of the duodenum; biopsies of the latter revealed an eroding pancreatic tumour with atypical cells consistent with a VIPoma. Measurement of the stool output and electrolyte content showed him to have a secretory diarrhoea: on a normal diet the stools weighed 415 g with a 24 hour electrolyte content of sodium 15 mmol, potassium 40 mmol (see Figure 1 period A) and on intravenous fluids with nil orally weighed 2800 g with 24 hour electrolyte content of sodium 339, potassium 51 mmol (period B). Even though the stool output was low on a normal diet for a patient with secretory diarrhoea the stool was watery, the increased stool output on intravenous fluids was a better reflection of his normal stool output. A gut

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hormone profile showed a raised VIP of 134 pmol/l (normal < 30 pmol/l) and pancreatic polypeptide of 1000 pmol/l (normal < 300 pmol/l).

He was given a trial of intravenous somatostatin analogue SMS 201–995 25 μg/h for 4 days (period C) to elucidate whether he was responsive, followed by subcutaneous SMS 201–995 50 μg twice daily with a normal diet for 7 days (see Figure 1); period D 0600 h and 1800 h, period E 0900 h and 2100 h – this second period was suited to his meal times.

Subcutaneous SMS 201–995 resulted in symptomatic improvement and passage of a formed stool. He also noticed less colicky pain on defaecation. On stopping the SMS 201–995 there was a rebound effect with a recurrence of watery diarrhoea (period F), increased stool output compared to when on SMS 201–995, and general ill-health. In view of the good therapeutic response he was started on 50 μg subcutaneous somatostatin SMS 201–995 twice daily (period G) with good effect and over 9 days learnt the injection technique, at which point we were able to discharge him home. Although there was little change in the stool weight, the stool became formed and he was asymptomatic. He has now been maintained on this regime for 24 months and his symptoms remain controlled. He has had no obvious side effects from SMS 201–995 and he opens his bowels twice a day with no pain. Over this period he has had five admissions with melaena due to bleeding from the tumour as diagnosed endoscopically, but after blood transfusion has returned home each time after 72 hours. A repeat ultrasound shows no increase in tumour size and a gut hormone profile showed that the VIP concentration was lower.

**Discussion**

Somatostatin was first isolated from the hypothalamus in 1972, originally thought to be a specific hypothalamic factor modulating the release of growth hormone, but now known to have a widespread action inhibiting secretion of growth hormone, thyrotrophin, gastrin, gut hormones, insulin and glucagon. Raptis et al. showed that somatostatin reduced plasma concentrations of gut hormones when infused intravenously. These findings suggested a therapeutic use for somatostatin in unresectable gut hormone producing tumours, but the major disadvantage was

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**Figure 1** Graph showing stool weight v. days. A: Normal diet; B: intravenous fluids – nil by mouth; C: intravenous SMS 201–995 – nil by mouth; D: subcutaneous SMS 201–995 0600 h, 1800 h; E: subcutaneous SMS 201–995 0900 h, 2100 h; F: SMS 201–995 stopped/normal diet; G: subcutaneous SMS 201–995 0900 h, 2100 h.
the short half-life of somatostatin of less than 3 minutes.⁴ Further work on somatostatin analogues with a longer half-life showed that gut hormone levels and stool volume could be reduced by administration both intravenously and subcutaneously.⁷⁻¹⁰ Long acting somatostatin analogues have now been used for the treatment of life-threatening diarrhoea⁶ and in one case caused shrinkage of the tumour.¹¹ The mechanism of action is not known; flow studies demonstrate increased jejunal and ileal fluid absorption, increased potassium and chloride absorption and reversed sodium secretion, but these changes do not occur when somatostatin is given to healthy controls.¹² It is unlikely that somatostatin acts entirely by direct stimulation of water and electrolyte absorption in the intestine, but more probably by either inhibition of tumour hormone release or by inhibition of the effect of tumour hormone on the intestinal mucosa.

The use of somatostatin analogue is now well recognized but there have been few reports on the use for long-term management.¹³,¹⁴ The patient we report leads an active life and is able to pursue hobbies, having no problems with incontinence. We have avoided major surgery and controlled his symptoms with no side effects. We therefore feel treatment with somatostatin analogue SMS 201–995 is useful in patients where surgery is contraindicated and side effects are encountered with streptozotocin and can be used in the long term with no deleterious effects.

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References

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