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CASE REPORT

Effective treatment of diabetic diarrhoea with somatostatin analogue, octreotide

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Abstract

A 22 year old insulin dependent diabetic with high volume, secretory chronic diarrhoea refractory to standard andiarrhoeal drugs was treated with the somatostatin analogue octreotide, 50 μg twice daily by subcutaneous injection. She improved markedly with a decrease in mean stool weight from 1170 g/24 h range 440–2900 g) to 440 g/24 h (range 180–800 g) ($p<0.05$). Stool frequency also decreased from six (range two to 12) to one (range one to three) bowel movements per day ($p<0.01$). Mouth to caecum transit time increased from 45 minutes to >210 minutes, although total gut transit time was unchanged and remained rapid at nine hours. Thus octreotide can reduce stool volume and frequency in high volume diabetic diarrhoea when conventional antidiarrhoeal agents have failed. Its therapeutic benefit appeared to be predominantly related to a marked increase in mouth to caecum transit time.

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Diabetic diarrhoea is a common complication of insulin dependent diabetes mellitus.[1] High volume watery diarrhoea in diabetics may be chronic and refractory to conventional antidiarrhoeal treatments. The mechanisms involved are complex and often multifactorial. In diabetics with severe autonomic neuropathy in whom small intestinal and pancreatic disease has been excluded and bacterial overgrowth ruled out, neurological damage directly or indirectly to the enteric nervous system is thought to be an important factor.[2] The enteric nervous system is not only important for controlling intestinal motility but also for modulating intestinal secretory and absorptive processes. The somatostatin analogue, octreotide, has been found to be effective in the treatment of chronic refractory diarrhoea caused by AIDS enteropathy,[3] short bowel syndrome[4] and idiopathic secretory diarrhoea.[5] A trial of octreotide was recently successful in controlling severe diarrhoea in two diabetic patients.[6,7] We now report a patient with high volume diabetic diarrhoea who responded to octreotide and have attempted to define its mode of action.

Case report

A 22 year old woman with insulin dependent diabetes mellitus for seven years was admitted on several occasions to Queen Alexandra Hospital, Portsmouth and later transferred to St Bartholomew's Hospital, with chronic, watery diarrhoea of two years duration. Bowel frequency was particularly troublesome at night (up to three) and two to nine times during the day. The diarrhoea had become progressively worse six months before presentation during which time she lost 14 kg in weight (25% usual body weight). She had failed previously to respond to antibiotics (including metronidazole and oral vancomycin), cholestyramine and pancreatic enzyme supplements. Similarly, there had been no improvement with the antidiarrhoeal agents, loperamide and codeine phosphate which had been used in high doses. The diabetes was complicated by retinopathy and painful peripheral neuropathy confirmed by abnormal nerve conduction studies. She also had autonomic neuropathy as shown by severe orthostatic hypotension with 50 mm Hg decrease in systolic blood pressure on standing, by absence of change in heart rate and electrocardiograph R-R interval during inspiration and Valsalva manoeuvre and by a positive skin wrinkling test.[8]

During admission stool output was 440–2900 g per day and failed to decrease during a 24 hour fast (700 g/24 h). Extensive investigations including multiple stool microscopy and cultures, colonoscopy, barium follow through examination and duodenal, jejunal and colonic biopsies were all normal. Faecal fat excretion was normal and reducing substances were not detected in stools. Stool osmotic gap (40 mOsmol) was within the normal range (0–50 mOsmol). Serum T_4 and thyroid stimulating hormone concentrations were normal. We failed to detect laxatives in blood, urine or stools. Gut hormones (vasoactive intestinal polypeptide, gastrin, glucagon, neurotensin), calcitonin and 24 hour urine 5HIAA were all normal. Glucose hydrogen breath test and aerobic and anaerobic duodenal fluid cultures did not reveal evidence of bacterial overgrowth.

The most obvious abnormalities detected were rapid small and whole gut transit times. Mouth to caecum transit time measured by lactulose hydrogen breath test using a standard meal with 40 ml lactulose was short at 45 minutes (normal range 87 (7)) and total gut transit time estimated by the radioopaque marker technique[9] was nine hours (normal range 24–48 hours). A prolonged (17 hour) small intestinal manometric study revealed migrating motor complexes with normal periodicity. The phase III activity fronts

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propagated rapidly with a mean velocity of 15 cm/minute (normal 5 (2·3), n=10) in the proximal jejunum, and 7·5 cm/min (normal 3·4 (1·9), n=10) in the distal jejunum. The contractile frequency within the phase III front was increased at 13 contractions per minute (normal 11·5 (1·9)) in the proximal jejunum and 12 contractions per minute (normal 10·3 (0·3)) in the distal jejunum. Water absorption from 30 cm segment of jejunum perfused with a plasma electrolyte solution (Na 140, K 4, Cl 140, HCO_3 40 mmol/l) using a triple lumen catheter[10] was normal (2 ml/cm/h; normal 1–4) and increased appropriately with the addition of glucose (90 mmol/l) and glucose polymer (18 mmol/l) (2·5 and 5·1 ml/cm/h, respectively). Reference values in healthy volunteers for transit, motility and perfusion studies were obtained from studies done in the Department of Gastroentrology, St Bartholomew's Hospital by identical techniques to those described for this patient.

A diagnosis of idiopathic diabetic diarrhoea was made by exclusion and because all conventional therapies had failed to improve her symptoms, a trial of octreotide 50 μg subcutaneously was started twice daily. Stool frequency and weight decreased (Table, Figure) and stools became well formed. Mouth to caecum transit time increased to more than 3·5 hours but there was no change in the total gut transit time. On the day when octreotide was started she had an episode of hypoglycaemia and subsequently insulin requirements decreased by approximately 25%. When octreotide was withdrawn for a few days, stool output and bowel frequency returned to previous levels (Figure). In view of previous reports[11] we also attempted to control the diarrhoea with clonidine 0·3 mg orally every 12 hours; however, there was no change in stool weight or frequency (Figure). Octreotide was recommenced to good effect. After six months follow up she remains well, has gained 4 kg in weight and stool volume continues to be acceptable at 420 g/24 hours (range 0–620) and bowel frequency at 0–2/24 hours.

Discussion

The pathogenesis of high volume diabetic diarrhoea remains poorly understood. It is thought that damage to the intestinal autonomic nervous system and especially loss of stimulation of alpha adrenergic receptors on the enterocytes may play an important role by affecting both motility and water absorption. The high volume diarrhoea in our patient failed to improve while fasting implying a secretory type of diarrhoea. Water and electrolyte absorption, however, were normal in a 30 cm segment of jejunum assessed by triple lumen perfusion. This does not exlude the possibility that a secretory state existed more distally in the ileum or colon. As part of her generalised autonomic neuropathy we were able to detect severe disturbance of small bowel motility as evidenced by a reduced mouth to caecum transit time and increased rate of small intestinal propulsive activity measured manometrically.

In general, the treatment of diabetic diarrhoea has proved so far to be unrewarding, and many therapeutic trials using known antidiarrhoeal agents have failed to improve the incapacitating diarrhoea in these patients. Despite the rapid transit time in our patient, she failed to respond to drugs such as codeine phosphate and loperamide that slow intestinal motility. Because of the loss of intestinal adrenergic innervation in diabetic patients, clonidine and lidamidine which are alpha 2 adrenergic agonists have been found to be beneficial in the treatment of diabetic diarrhoea probably by stimulating the alpha 2 adrenergic receptors on enterocytes.[11,12] Our patient, however, failed to respond to clonidine. Octreotide has been previously reported to be beneficial in the treatment of other refractory diarrhoeas including AIDS enteropathy, short bowel syndrome and idiopathic refractory diarrhoea. Animal and human studies suggest that it acts by enhancing water and sodium absorption from the small intestine,[13] by inhibiting chloride secretion in the colon[14] and by prolonging mouth to caecum transit time.[15] Its mode of action in diabetic diarrhoea, however, has not been extensively studied. Octreotide reduced stool weight and frequency in our patient, and the stools became well formed. In addition, she had a remarkable subjective improvement and for the first time in two years she was able to conduct a normal life socially and professionally. Although the total gut transit time did not change, octreotide prolonged mouth to caecum transit time almost five-fold, presumably allowing greater small intestinal water absorption. The proportional increase in mouth to caecum transit time in this patient is greater than our previous observations in healthy volunteers (2·6-fold), although the absolute values of mouth to caecum transit time during octreotide treatment were similar (210 *v* 212 minutes, respectively).

In conclusion, this diabetic patient with high volume watery diarrhoea responded to octreotide confirming the findings of previous case reports.[6,7] Our studies suggest that prolongation of mouth to caecum transit time is an important component of its therapeutic effect in diabetic diarrhoea. Thus, octreotide therapy should be considered in intractable diabetic diarrhoea.

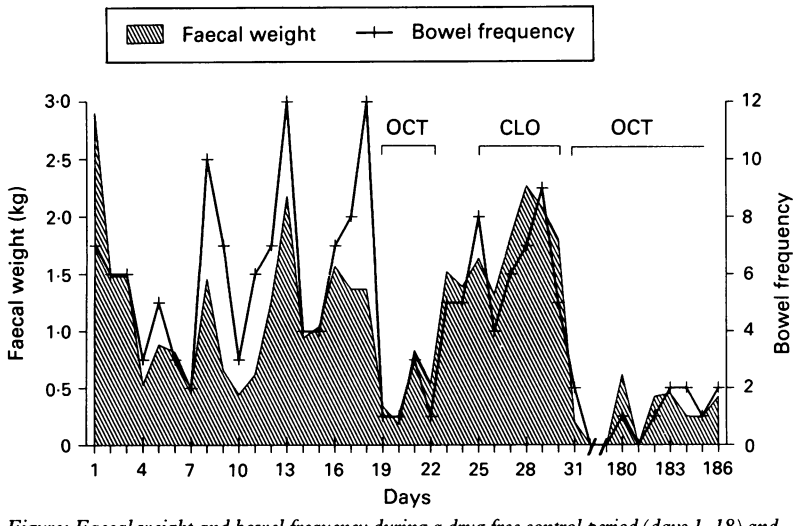

Figure: Faecal weight and bowel frequency during a drug free control period (days 1–18) and after treatment with octreotide 50 μg sc twice daily and clonidine 0·3 mg orally twice daily.

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