



Successful treatment of diabetic autonomic diarrhoea with monthly subcutaneous lanreotide

TJ Ulahannan*, A Amaratunga

Introduction

Diabetes mellitus (DM) can cause autonomic nervous system disease in many systems in long standing type 1 or type 2 DM. The most common gastrointestinal (GI) symptoms of autonomic dysfunction in DM are gastroparesis or alterations in small and large bowel motility (constipation/diarrhoea). Treatment options for diabetic autonomic diarrhoea (DAD) are limited¹ and directed at symptom control. We describe a case of refractory DAD successfully treated with the octreotide analogue lanreotide.

Case report

A 29-year-old woman presented to her general practitioner with six months' deterioration in watery diarrhoea, onset six years before. She had poorly controlled type 1 DM for 15 years with multiple complications. There was no recent history of laxative abuse, medication change, dietary alteration, travel, or contacts with similar symptoms. There was no family history of GI disorders or malignancy. Current medications were codeine phosphate and loperamide.

Bowels opened 40 times per 24 hours, with nocturnal faecal incontinence, urgency, tenesmus, 6kg weight loss, swinging blood glucose levels, and malaise. Bowels opened within 40–60 minutes of any food or drink consumption. Stools were watery, voluminous and brown coloured. No blood, mucus, nausea, vomiting or abdominal pain was reported. Symptoms

ABSTRACT

A 29-year-old woman, with 15 years of poorly controlled type 1 diabetes and established diabetic autonomic diarrhoea, presented with worsening diarrhoea and diabetic ketoacidosis. Frequency of bowel opening was up to 40 times per 24 hours. Octreotide was started, rapidly decreasing bowel motion frequency. Due to previous intolerable side effects of rotten odour breath and flatus, she converted to once-monthly subcutaneous lanreotide (Somatuline Autogel). Her diarrhoea remained controlled without any side effects, until her demise a year later from severe diabetic ketoacidosis.

To our knowledge this is the first published report of the successful treatment of intractable diabetic autonomic diarrhoea by once-monthly subcutaneous lanreotide. Copyright © 2009 John Wiley & Sons.

Practical Diabetes Int 2009; 26(8): 326–328

KEY WORDS

autonomic neuropathy; diabetes; diarrhoea; lanreotide

were not relieved by conventional antidiarrhoeals.

She was admitted with two days' history of worsening diarrhoea, fever, rigors and raised blood glucose. On examination she appeared pale and cachectic. Investigations showed ketoacidosis, anaemia, leucocytosis and acute renal failure (glucose 17.4mmol/L, Hb 7.2g/dL, WCC 14.4x10⁹/L, C-reactive protein 90g/L, creatinine 720µmol/L, albumin 26g/L). Ketoacidosis, renal failure and infection were appropriately treated. After dietitian review, nasogastric semi-elemental feed was commenced to improve her nutritional status.

Tables 1 and 2 summarise the results of prior investigations and autonomic evaluation – the latter confirming evidence of autonomic neuropathy affecting both the sympathetic and parasympathetic nervous systems and cardiovascular function, with additional evidence of sudomotor and somatic neuropathy.

All investigations were reviewed at a tertiary referral centre. Table 3 summarises the patient's glycaemic control history.

Due to the recent, severe deterioration in diarrhoea, subcutaneous (SC) octreotide was given and this rapidly reduced bowel motion frequency. Due to previous intolerable flatulence and breath that smelt like 'rotten eggs' with octreotide this was changed to lanreotide, once clinical response was obvious (Somatuline Autogel 60mg monthly SC injections). She maintained good response, bowel frequency reduced to five per 24 hours within five days. The dose was increased to 90mg every 28 days, and within a month bowel frequency had reduced further to once every 48 hours (see Figures 1 and 2). Importantly, this formulation of the somatostatin analogue did not cause the side effects she had experienced previously whilst using octreotide injections.

Thomas J Ulahannan, FRCP, Consultant Physician, Gloucestershire Royal Hospital, Gloucester, UK

Ashwini Amaratunga, MBChB, Faculty of Medicine and Dentistry, University

of Bristol, Bristol, UK

*Correspondence to: Dr Thomas Ulahannan, FRCP, Consultant Physician, Gloucestershire Royal Hospital,

Gloucester GL1 3NN, UK; e-mail: Thomas.Ulahannan@glos.nhs.uk

Received: 22 March 2009

Accepted in revised form: 20 May 2009



Successful treatment of diabetic autonomic diarrhoea with monthly SC lanreotide

Table 1. Prior investigations

Investigation	Result
Stool culture	Normal
Endoscopy	Normal
Colonoscopy	Normal
Terminal ileal and colonic biopsy	Normal
72-hour faecal fat collection	Slight non-significant increase
Barium follow through	Increased gut transit time (40mins)
Gut hormone profile	Normal gastrin, secretin, somatostatin, VIP
Pancreolauryl test	Normal
CT abdomen	Normal viscera and bowels
¹⁴ C glycocholate breath test	Normal
Urinary 5H1AA	Normal
MRI brain	Normal
HbA _{1c}	18.4%
Full blood count	Hb 10.8g/dl, low MCV, MCH, MCHC
Liver, bone profile, magnesium, thyroid function	Normal

VIP = vasoactive intestinal peptide; MCV = mean cell volume; MCH = mean cell haemoglobin; MCHC = mean cell haemoglobin concentration.

Table 2. Prior autonomic evaluation

Test	Result
Sinus arrhythmia	Absent
Head up tilt	Failure to elevate normal basal plasma noradrenaline and adrenaline levels
24-hour blood pressure	Daytime mean of 109/71mmHg, elevated nocturnal mean 116/76 mmHg
Heart rate (HR)	Daytime mean 115bpm, nocturnal mean 110bpm
Orthostatic hypotension	Present 78/48mmHg, HR of 122bpm
Gustatory sweating	Unpredictable
Neurophysiology	Severe abnormalities with nerve conduction and thermal thresholds, all consistent with diabetic large and small fibre peripheral neuropathy

Control of diarrhoea without side effects was maintained over the next six months, until her demise from severe diabetic ketoacidosis despite maximal intervention.

Discussion

Diarrhoea in diabetes can result from the usual infectious causes, coeliac disease and bile salt diarrhoea as well as various drugs such as metformin, proton pump inhibitors and statins. Diabetic diarrhoea itself is a poorly recognised and poorly understood complication of diabetes – most

frequently, but not exclusively, affecting patients with poorly controlled type 1 DM, who also have evidence of diabetic peripheral and autonomic neuropathy. Its overall incidence has been reported to vary from 10–22%,^{2,3} and is more common in men than in women (3:2).³ It is chronic, of unknown aetiology and refractory to conventional treatment and is a diagnosis of exclusion. The major causative factor appears to be the co-existence of autonomic neuropathy,³ as in this case. In contrast to microvascular complications of

Table 3. Glycaemic control history

Date	HbA _{1c} (%) normal range 4.0–6.5%
August 2002	14
July 2003	17.3
June 2004	17.3
February 2005	17
June 2005	12.9
August 2005	12.9
October 2006	10
November 2006	9.5

diabetes,⁴ case studies show achievement of satisfactory blood glucose control is ineffective at alleviating DAD.³ Multiple conventional anti-diarrhoeals have been tried with variable success.^{3,5} The various agents tried over six years in our patient are shown in Figure 1. Response was poor, and generally short-lived (see Figure 1). Octreotide eight-hourly SC injections then lanreotide (Somatuline Autogel) produced the best response (Figures 1 and 2).

Lanreotide and octreotide are identical octapeptide analogues of natural somatostatin. They exhibit: a general exocrine anti-secretory action inhibiting the basal secretion of motilin, gastric inhibitory peptide and pancreatic polypeptide; inhibition of meal-induced increases in superior mesenteric artery blood flow and portal venous blood flow; and reduction of prostaglandin E₁-stimulated jejunal secretion of water, sodium, potassium and chloride. They are useful in a variety of diarrhoea states and have similar affinity for the somatostatin receptor subtypes SSTR1–SSTR5 with a longer half-life due to slower plasma degradation.^{6–9}

Somatuline Autogel (lanreotide) is a slow release formulation of microspheres, which constantly expel small amounts. After SC injection, maximum serum concentration is reached after six hours, followed by a slow decrease (mean residence time: 30±6 days; apparent half-life: 33±14 days). In contrast, an SC injection of Sandostatin (octreotide) achieves peak plasma concentrations in 30 minutes with a half-life of 100 minutes.⁸

CASE REPORT



Successful treatment of diabetic autonomic diarrhoea with monthly SC lanreotide

Figure 1. Effect on bowel frequency

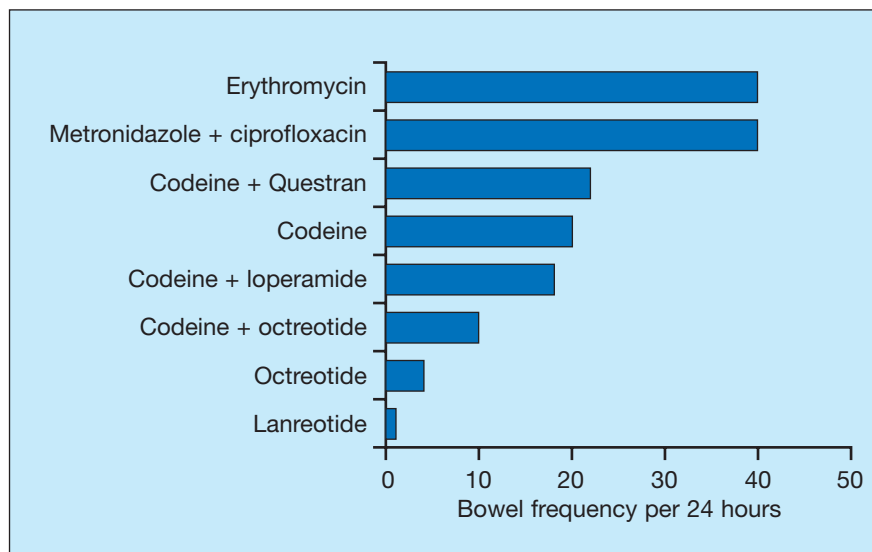
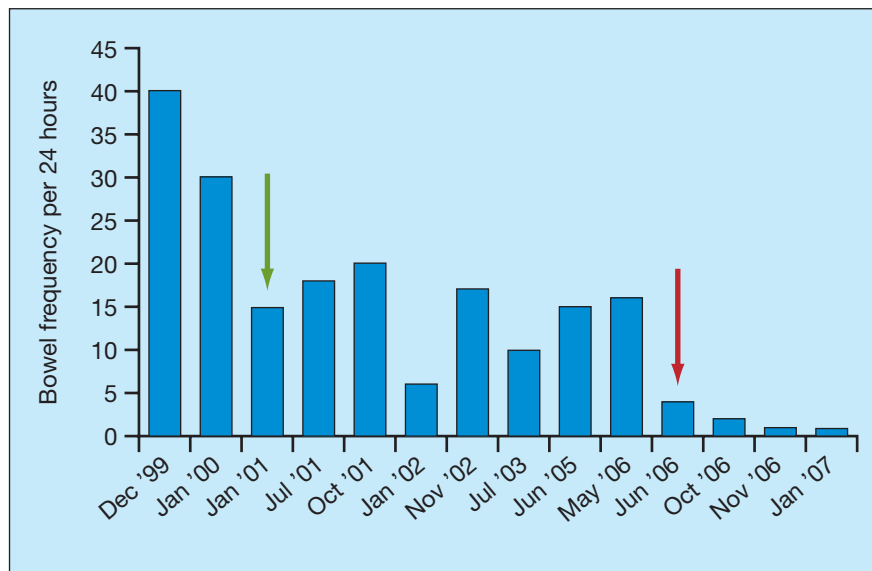


Figure 2. Efficacy of various antidiarrhoeal treatments. (Green arrow indicates start of SC octreotide bd/tds; red arrow indicates start of lanreotide once every 28 days)



Octreotide given with insulin in type 1 DM without diabetic diarrhoea or autonomic neuropathy has shown no effects on glucose or HbA_{1c}, but induced diarrhoea in a dose-dependent fashion.¹⁰ Sandostatin LAR suppressed glucagon-like peptide-1 (GLP-1) secretion in obese type 2 DM.¹¹ GLP-1 administered in type 1 DM reduced post-prandial glucose, gastric emptying and glucagon concentrations,¹² but data on the effects of octreotide on this response are lacking.

Diabetic autonomic neuropathy patients can have abnormally rapid gastric emptying and transit

through the distal small bowel. Octreotide can induce activity similar to the interdigestive migrating motor complex in the small intestine followed by quiescence, thus prolonging transit time. The difference in side effects in this case may be due to the different pharmacokinetics and/or lanreotide having no effect on fasting gastrin or secretin secretion unlike octreotide. Rotten egg odour in flatus is due to the presence of hydrogen sulphide arising from protein breakdown. Octreotide inhibition of fasting gastrin and secretin might have led to more protein breakdown in the

Key points

- Diabetic autonomic diarrhoea (DAD) can be a debilitating complication of poorly controlled diabetes
- DAD usually occurs with other autonomic system complications
- DAD responds poorly to conventional antidiarrhoeals except octreotide
- In this case octreotide, while effective, caused intolerable side effects
- Lanreotide (Somatuline Autogel) was able to give the benefits of octreotide without side effects with a single monthly injection and, to our knowledge, has not previously been reported as a treatment for DAD

gut to release flatus. The reduction in diarrhoea does seem to be dose responsive with 90mg of lanreotide having a greater effect than 60mg.

Conclusions

Clinical results in this patient showed a valuable effect of lanreotide, after demonstrating octreotide responsiveness, in debilitating diabetic diarrhoea unresponsive to conventional treatments. As well as the great benefit from reduction in diarrhoea, only one injection per month was required compared to thrice daily with octreotide and without the very unpleasant side effects previously suffered. This benefit was observed despite the long history of poorly controlled diabetes with multiple complications and unresponsiveness to conventional treatments for diarrhoea. This produced a valuable improvement in this patient's quality of life, though ultimately she succumbed to diabetic ketoacidosis. This appears to be the first published case of treatment of refractory diabetic diarrhoea by lanreotide (Somatuline Autogel).

Conflict of interest statement

AA has no conflict of interest. TJU has received meeting sponsorship from Ipsen.

References

References are available at www.practicaldiabetesinternational.com.



Successful treatment of diabetic autonomic diarrhoea with monthly SC lanreotide

References

1. Nakabayashi H, Fujii S, Miwa U, *et al.* Marked improvement of diabetic diarrhea with the somatostatin analogue octreotide. *Arch Intern Med* 1994; **154**: 1863–1867.
2. Feldman M, Schiller LR. Disorders of gastrointestinal motility associated with diabetes mellitus. *Ann Intern Med* 1983; **98**: 378–384.
3. Ogbonnaya KI, Arem R. Diabetic diarrhoea pathophysiology, diagnosis and management. *Arch Intern Med* 1990; **150**: 262–267.
4. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329**: 977–986.
5. Mourad FH, Gorard D, Thillainayagam AV, *et al.* Effective treatment of diabetic diarrhoea with somatostatin analogue, octreotide. *Gut* 1992; **33**: 1578–1580.
6. Reichlin S. Somatostatin. *N Engl J Med* 1983; **22**: 1556–1564.
7. Farthing MJG. The role of somatostatin analogues in the treatment of refractory diarrhoea. *Digestion* 1996; **57**(Suppl 1): S107–S113.
8. Electronic Medicines Compendium. Available at: www.emc.medicines.org.uk/.
9. Katzung BG. *Basic & Clinical Pharmacology*, 8th edn. USA: McGraw-Hill, 2001.
10. Osei K, O'Dorisio TM, Malarkey WB, *et al.* Metabolic effects of long-acting somatostatin analogue (sandostatin) in type I diabetic patients. *Diabetes* 1989; **38**: 704–709.
11. Velasquez-Mieyer PA, Umpierrez GE, Lustig RH, *et al.* Race affects insulin and GLP-1 secretion and response to a long-acting somatostatin analogue in obese adults. *Int J Obesity* 2004; **28**: 330–333.
12. Behme MT, Dupré J, McDonald TJ. Glucagon-like peptide-1 improved glycemic control in type 1 diabetes. *BMC Endocr Disord* 2003; **3**: 3. Published online 10 April 2003; doi: 10.1186/1472-6823-3-3.