

Successful treatment of obesity and diabetes with incretin analogue over four years in an adult with Prader–Willi syndrome

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Abstract

A 36-year-old female diabetic patient with genetically confirmed Prader–Willi syndrome had developed weight increase and severe symptomatic hyperglycaemia despite triple oral hypoglycaemic therapies. Main meals were supervised at home and when working in day care. The addition of insulin therapy induced further weight increase and hypertension with only a small improvement in glycaemia. She suffered from a thrombotic stroke.

During rehabilitation her hyperphagia persisted and she was commenced on exenatide in addition to insulin and oral hypoglycaemic agents. Incretin analogue therapy was well tolerated after brief initial nausea. Improved glycaemia allowed insulin to be phased out after six months. General well-being, weight, blood pressure, microalbuminuria, glycosylated haemoglobin, and serum lipids all showed sustained improvement. Despite concerns about hyperphagia and resultant severe vomiting in Prader–Willi syndrome, our patient responded safely to incretin analogue therapy. Weight loss and metabolic improvements have been sustained for four years. Copyright © 2011 John Wiley & Sons.

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Key words

incretin analogue; type 2 diabetes; Prader–Willi syndrome

Introduction

Prader–Willi syndrome (PWS) is associated with severe childhood onset obesity in the context of hyperphagia and low metabolic rate [MIM 176270 601491].^{1,2} Although type 2 diabetes occurs commonly in early middle life,^{3–6} this is associated with relatively normal insulin sensitivity and lower insulin resistance compared to weight matched individuals without PWS. Bingeing on food, the low metabolic rate and reduced insulin secretion could prevent a satisfactory response to incretin analogue therapy which acts by slowing gastric emptying, enhancing insulin action and inducing satiety.^{7,8} In our patient, oral agents and insulin caused worsening obesity, severe metabolic dysfunction and hypertension culminating in a stroke. A trial of exenatide therapy was undertaken.

Case report

A 36-year-old, right-handed female with PWS, living in sheltered accommodation and in day care presented with sudden onset right hemiparesis and dysphasia. She had never received growth hormone therapy, or oestrogenic hormones. Genetic confirmation of the diagnosis had

been made in childhood (46, XX.ish del (15)(q11.2q11.2) (SNRPN-)).

She had developed type 2 diabetes 10 years previously and, despite nutrition management by a carer, regular walks and escalation of oral hypoglycaemic agents (including metformin, gliclazide and rosiglitazone), her weight increased from 72 to 78 kg and blood pressure from 130/80 to 150/90 mmHg. Biphasic insulin was added to control osmotic symptoms and rosiglitazone stopped. This resulted in further weight increase to 83 kg (BMI 33), culminating after six months with the stroke. CT scan of the brain on admission showed ‘an area of low density in the left internal capsule consistent with an infarct’.

After a complete recovery from the stroke her craving for sweet foods, especially cakes and confectionary, persisted. She remained tired with thirst and urinary frequency. Discussions with the patient, her carer and her mother established that she had capacity to consider treatment with an incretin analogue in addition to insulin, metformin and gliclazide. She gave signed consent to this, with the understanding that the therapy should be discontinued if severe sickness and vomiting were to

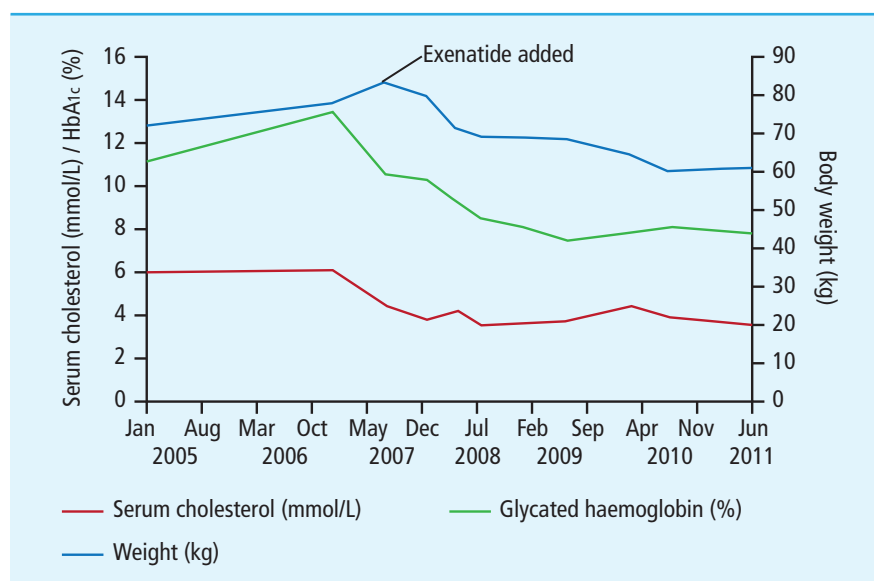


Figure 1. The patient's changes in weight, glycaemia and serum cholesterol during exenatide therapy over four years after stroke in Prader–Willi syndrome

occur. Exenatide 5µg twice-daily was commenced and increased in outpatient consultation to 10µg twice-daily after one month. Nausea occurred transiently without vomiting during the first week of therapy.

During the first six months of incretin therapy, insulin was reduced and then withdrawn due to improvement in well-being, reduction in hyperphagia and loss of weight to 71.3kg. Waist circumference had decreased from 120 to 115cm. One year after commencement of the incretin analogue the patient's menstrual cycles returned for the first time in 10 years and gliclazide was phased out over the next year.

The clinical improvement was consolidated during the next 36 months – weight 60kg (BMI 29.8), waist 103cm, and blood pressure 130/80mmHg. She returned to day care, daily walks and a comfortable eating pattern under supervision. Annual retinal screening confirmed a stable background retinopathy throughout. Her comment has been 'this treatment has given me my life back'.

Figure 1 shows body weight, glycated haemoglobin and serum cholesterol before and for four years after the commencement of exenatide. Serum triglycerides, HDL cholesterol and urine microalbumin/creatinine ratio all improved over the four years: 2.2 to 1.4mmol/L; 0.86 to 1.10mmol/L; 16.3 to 5.7µg/mmol respectively.

Discussion

Prader–Willi syndrome is characterised by severe hyperphagia with progression to obesity in virtually all cases, resulting in type 2 diabetes in 20%.¹ Life expectancy is reduced because of vascular disease and propensity to infection.⁹

In this case study, incretin analogue therapy has been associated with remission in hyperphagia, obesity and hyperlipidemia and substantial improvement in diabetes control. This has permitted withdrawal of insulin and sulphonylurea. The condition is considered to exhibit low metabolic rate and an hypothalamic cause of increased appetite, with no evidence of increased insulin resistance.^{2–6} These characteristics suggest that response to incretin analogue therapy might be limited. However, recent studies have demonstrated increased levels of the orexigenic gut hormone ghrelin and impaired PYY release in adults with the syndrome, which may contribute to the hyperphagia. Post-prandial suppression of ghrelin levels was not restored when exenatide was administered pre-prandially in a meal study of PWS subjects and obese matched controls, though insulin secretion and satiety were improved.^{10–12} There is a concern that food binges may provoke severe vomiting with incretin analogues.^{9,13} The success of this therapy in our case without significant side effects gives rise to cautious optimism that

Key points

- An intermediate form of diabetes occurs in 20% of adults with Prader–Willi syndrome
- Vascular disease contributes to mortality. Long-term metabolic improvement has been shown with incretin analogues in this case without side effects

other adults with Prader–Willi syndrome and glucose intolerance might benefit from incretin analogue therapy. A clinical trial would be justified with very careful monitoring of eating behaviour.

Acknowledgement

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Declaration of interests

There are no conflicts of interest declared.

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