Effects of octreotide on circulating islet B cell products in endogenous hyperinsulinism

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Summary: The role of somatostatin analogues in the medical management of insulinomas is unclear. We describe an elderly patient with clinical and biochemical features of endogenous hyperinsulinism attributable to a benign islet B cell disorder whose incapacitating neuroglycopenic symptoms responded dramatically to octreotide 50 µg subcutaneously at 2200 h each night. Octreotide suppressed inappropriate plasma concentrations of insulin thereby preventing fasting hypoglycaemia. Fasting concentrations of proinsulin, and 32–33 split proinsulin, as determined by two-site monoclonal antibody-based immunoradiometric assays, were also suppressed by octreotide.

Introduction

Surgical excision remains the definitive treatment for benign functioning insulinomas^{1,2} with long-term medical treatment usually being reserved for patients who refuse surgery or those in whom surgery is deemed inappropriate.³ However, the therapeutic options for medical management of endogenous hyperinsulinism remain relatively limited. The anti-hypertensive agent diazoxide has been used successfully to inhibit insulin secretion by insulin-secreting tumours but is commonly associated with significant adverse effects including fluid retention and hirsutism.⁴ The efficacy of alternative drugs such as verapamil and beta-blockers remains unclear.⁴

Octreotide is a long-acting analogue of somatostatin with potent suppressive effects on a number of endogenous hormones including insulin.^{5,6} However, the role of octreotide in the management of benign insulinomas remains to be clarified. The literature contains conflicting reports of efficacy⁷ contrasting with worsening of fasting hypoglycaemia.^{4,8–10} We describe an elderly man with clinical and biochemical features of an insulin-secreting tumour whose symptoms were abolished by a single nightly dose of octreotide. Octreotide suppressed fasting concentrations of circulating insulin and islet B cell conversion intermediates thereby preventing hypoglycaemia.

Methods

Plasma immunoreactive insulin,¹¹ proinsulin, and C-peptide concentrations were determined using double antibody radioimmunoassays (RIAs). Plasma concentrations of insulin, proinsulin, and 32–33 split proinsulin were determined using highly specific two-site monoclonal antibody-based immunoradiometric assays (IRMAs) with between assay coefficients of variation (CVs) of 15% or less and detection limits ranging from 0.8 to 2.5 pmol/l.¹² Venous plasma glucose concentrations were determined using glucose oxidase methods on fluoride-oxalate samples.

Patient

An 80 year old man presented with a 2 week history of episodic confusion and agitation occurring each morning before breakfast. Two weeks earlier he had undergone a transurethral prostatectomy for benign disease which was complicated by an acute postoperative Gram-negative septicaemia. Past medical history included asymptomatic chronic atrial fibrillation treated with digoxin. There was no other relevant drug history nor any history of alcohol consumption.

Physical examination revealed an afebrile patient with a body mass index of 24 kg/m² and an irregular pulse. Atrial fibrillation was confirmed by electrocardiography; chest and abdominal radiology were unremarkable. Blood leucocyte count was normal. Computerized tomography (CT) revealed no significant intracranial abnor-

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malities although electro-encephalography revealed an abnormal record suggestive of a generalized metabolic disorder. Early one morning shortly after admission the patient was discovered unrousable in bed. Capillary blood glucose concentration measured at the bedside using a reflectance meter was 2.0 mmol/l. The administration of glucagon 1 mg subcutaneously was followed by a rapid improvement in level of consciousness. This pattern of events was repeated on subsequent mornings with fasting venous blood glucose concentrations of 1.9 mmol/l and 1.8 mmol/l in concert with plasma immunoreactive insulin concentration (RIA) of 102 pmol/l and 45 pmol/l (normal <15 pmol/l), respectively. Fasting plasma C-peptide concentration was inappropriately normal at 528 pmol/l during hypoglycaemia with an elevated plasma proinsulin concentration (RIA) of 30 pmol/l (normal <10). Alternative causes of fasting hypoglycaemia were excluded as far as possible: renal and hepatic function were normal on routine biochemical screening, and plasma cortisol response to 250 µg Synacthen was normal. There were no suspicious features to suggest surreptitious sulphonylurea consumption. The temporal relationship between the onset of hypoglycaemic symptoms and the antecedent septicemic illness appeared to be consistent with reduced caloric intake resulting in hitherto borderline fasting hypoglycaemia becoming clinically overt.

Ultrasound and CT scanning with contrast enhancement, while providing good visualization of the pancreas, failed to localize a tumour. Thus the differential diagnosis lay between a small single insulinoma, diffuse adenomatosis, or adult nesidioblastosis.⁴ Medical therapy was therefore initiated with the objective of avoiding invasive investigations and the prospect of distal pancreatectomy if a tumour could not be identified at laparotomy. Diazoxide was considered to be relatively contraindicated by the presence of chronic cardiovascular disease. A trial of octreotide 50 µg subcutaneously at 2200 h was com-

menced after full explanation of the experimental nature of the treatment and possible adverse effects. The use of octreotide was approved by the Research Ethics Committee of South Birmingham Health Authority. The therapeutic effect of octreotide was dramatic with prompt resolution of all neuroglycopenic symptoms. Octreotide effectively suppressed inappropriately elevated fasting concentrations of insulin, proinsulin, and 32–33 split proinsulin thereby eliminating early morning hypoglycaemia (Table I). During the week following the introduction of octreotide fasting plasma glucose concentrations ranged between 4.0 and 7.0 mmol/l. To date, the patient has remained symptom-free on a single self-administered nightly dose during 12 months of follow-up with fasting blood glucose concentrations of 4.5–5.0 mmol/l. Octreotide has been well tolerated and no side-effects of therapy have been encountered.

Discussion

The biochemical diagnosis of insulinomas relies on the demonstration of inappropriate normal or elevated circulating insulin concentrations in the presence of fasting hypoglycaemia. Care should be taken to exclude the possibility of drug-induced hyperinsulinaemia, especially surreptitious medication with sulphonylureas.¹ The management of benign insulinomas comprises surgical excision wherever possible; long-term medical therapy is usually reserved for selected cases such as the patient reported here.

Somatostatin analogues have been successfully employed in the management of hyperinsulinaemia in infancy¹³ and in insulin-secreting tumours in adults.⁷ However, beneficial effects of octreotide have not been universally reported.⁴ Some patients with markedly elevated plasma immunoreactive insulin concentrations have shown no improvement.^{14,15} Suppression of counter-regulatory hormone secretion has been implicated in reports of exacerbation of hypoglycaemia during treatment

Table I Fasting venous plasma concentrations of glucose, insulin, and islet B cell conversion intermediates prior to, and on day 5 and day 6 following the initiation of octreotide 50 µg subcutaneously at 2200 h each night

	Glucose (mmol/l)	Insulin (pmol/l)	Proinsulin (pmol/l)	32–33 split pro- insulin (pmol/l)	Total (pmol/l)
<i>Pre-octreotide</i>					
	1.8	61	15.0	5.5	81.5
<i>Post-octreotide 50 µg at 2200 h</i>					
Day 5	5.8	24	6.0	<1.0	31.0
Day 6	5.3	21	5.4	<1.0	27.4

with octreotide.⁸ These caveats notwithstanding, several successful treatment regimens have been described including multiple daily subcutaneous injections^{4,9} and continuous subcutaneous infusion regimens.⁷

Approximately 80% of insulinomas are reported to secrete an excess of proinsulin relative to immunoreactive insulin.^{16,17} However, the literature concerning immunoreactive insulin and proinsulin concentrations in insulin-secreting tumours is largely derived from radioimmunoassays characterized by significant crossreactivity between insulin and proinsulin-like molecules.^{18,19} We therefore measured plasma insulin and islet B cell conversion intermediates using two-site immunoradiometric assays.¹² While the role of specific assays of proinsulin-like molecules in the diagnosis of insulinomas has yet to be clearly established several observations provide support for the diagnosis of insulinoma in our patient. First, fasting plasma insulin concentration was not suppressed in the presence of hypoglycaemia.²⁰ Second, fasting proinsulin concentration was elevated during hypoglycaemia.²¹ Similarly, the molar ratio of (proinsulin + 32–33 split proinsulin) to (insulin + proinsulin + 32–33 split proinsulin) expressed as a percentage was elevated at 25.1% compared to $9.4\% \pm 1.0$ (mean $\pm$ s.e. in healthy middle aged subjects).²² Third, the fasting plasma insulin: glucose ratio was elevated at 34% (normal: $10.1 \pm 1.0\%$),²² a biochemical feature characteristic of states of endogenous hyperinsulinism.⁴

Octreotide had a marked effect on circulating concentrations of islet B cell products with suppression of fasting concentrations of insulin, proin-

sulin, and 32–33 split proinsulin, the latter being suppressed below the detection limit of the assay. The ratio of total proinsulin-like molecules to insulin was not significantly altered by octreotide. Since proinsulin-like molecules are characterized by lower biological activities than insulin²³ it seems likely that suppression of insulin concentrations were primarily responsible for the improvement observed in fasting plasma glucose concentrations. Whether the response of an insulinoma to octreotide is dependent on the relative secretion of insulin or proinsulin-like molecules or whether the response of solitary islet B cell tumours is comparable with that of multiple islet adenomatosis or adult nesidioblastosis⁴ has not been determined.

In summary, a single nightly dose of octreotide eliminated fasting hypoglycaemia in our patient through suppression of circulating insulin concentrations. Fasting concentrations of proinsulin and 32–33 split proinsulin were also suppressed. The case reported indicates that octreotide can be an effective and well-tolerated long-term medical treatment for certain patients with endogenous hyperinsulinism.

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Cardiac arrest: a rare complication of pallid syncope?

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Summary: Cardiac arrest is rare in children. Breath-holding, on the other hand, is fairly common. We report a case in which one complicated the other with serious consequences. A review of the literature on the subject was undertaken.

Introduction

Pallid syncope (reflex anoxic seizure) is a fairly common childhood event that is probably under-recognized. It has been reported that 4.6–46.2% of a childhood population suffer breath-holding attacks of some form and 1% have pallid syncope, the others having the more commonly diagnosed and better understood cyanotic variety.¹ Pallid syncope is distinguished by the child's obvious pallor during the attack, together with other signs suggestive of vagal overactivity. In a small number of patients with very frequent attacks, treatment with atropine has been shown to be effective.²

The diagnosis can be further established by the demonstration of vagal asystole from eyeball compression, a procedure said to be safe and free of complications, the cardiac standstill being self-limiting.³

These events are often very dramatic and frightening to the parents, but fundamentally harmless; we report the case of a child with a previous history of attacks suggestive of pallid syncope, who suffered an unexplained cardiac arrest.

Case report

A 21 month old child had been entirely well in the past. He had a history of frequent episodes of breath-holding, starting at the age of about 6 months, during which he is said to have become profoundly pale and his parents report having been deeply alarmed by these in the past, although no hospital contact had resulted. The patient is the only child of the couple, neither of whom has a family history of breath-holding or sudden infant death syndrome.

On the occasion of his admission, he is said to have been well. His parents reported that they had had an argument during the early evening and a training shoe was thrown; this accidentally struck the child on the left side of the abdomen. He started to cry, held his breath, arched his back and his eyes rolled upwards. His father picked him up, only for him to become pale and limp.

One parent began mouth-to-mouth resuscitation whilst the other called an ambulance. The paramedically trained crew arrived 4 minutes later and found him in asystole. He was intubated and cardiopulmonary resuscitation was commenced in the ambulance *en route* to hospital; atropine and adrenaline were given via the endotracheal tube without success. The accident and emergency department was reached 25 minutes after the first call.

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