Case report

Diazoxide for the treatment of hypoglycaemic dumping syndrome

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Introduction

Dumping syndrome is a commonly recognized complication after gastric and oesophageal surgery.1 It is characterized by postprandial early gastrointestinal and vasomotor symptoms followed by late hypoglycaemia. Early dumping symptoms include abdominal pain, bloating, nausea, vomiting, flushing, tachycardia and hypotension. Late dumping symptoms which occur 1–3 h after food are thought to be due to excess insulin secretion that results in hypoglycaemia. Management of hypoglycaemia in dumping syndrome can be challenging and the therapeutic options are dietary modifications, acarbose, octreotide and diazoxide all providing varying degrees of symptomatic relief.1 Dumping syndrome is likely to become more prevalent due to the pandemic of obesity and associated use of bariatric surgery. Diazoxide has been occasionally used with some success in post-bariatric surgery dumping syndrome2 but there are no reports of its effective use in treating hypoglycaemia associated with primary gastric surgery. We describe three patients with hypoglycaemic dumping syndrome after different gastric surgeries that were successfully treated with diazoxide.

Case histories

Case 1

An 80-year-old man with a history of partial gastrectomy and pyloroplasty for peptic ulcer disease 30 years ago presented with symptoms suggestive of hypoglycaemia extending over nearly 15 years. He reported episodes of confusion, disorientation, sweating and dizziness a few hours after meals which were resolved by sugary food and drinks. A prolonged glucose tolerance test (GTT) confirmed postprandial hypoglycaemia (Table 1). He was referred to a dietician and advised to space carbohydrate intake throughout the day (small and frequent meals up to five or six times a day). His adherence to dietetic advice was variable and the symptoms persisted. He was prescribed acarbose that reduced the frequency of hypoglycaemia but had to be discontinued due to persistent bloating and abdominal pain. He was then given a trial of diazoxide 50 mgs twice daily, on which he has remained free of hypoglycaemic symptoms for the past 2 years. His HbA1c ranged from 6.9% to 7.4% (52–57 mmol/mol) prior to treatment is now 7.2% (55 mmol/mol). He had a past medical history of ischaemic heart disease, aortic valve disease and left ventricular dysfunction for which he was on anti-anginal treatment and furosemide (40 mg daily) prior to starting diazoxide. He continues on the same dose of diuretic with no further increase in peripheral oedema.

Case 2

An 81-year-old lady who had a vagotomy with pyloroplasty for peptic ulcer disease many years ago reported several episodes of tremors and dizziness resolved by fast acting carbohydrate. A prolonged GTT was suggestive of postprandial
hypoglycaemia (Table 1) and she was given dietary advice as described in Case 1, with only marginal improvement in symptoms. She was unable to tolerate doses >50 mgs daily of acarbose and was therefore commenced on diazoxide 50 mgs twice daily. She has remained free of hypoglycaemia for the past 4 years. Twelve months after initiation of diazoxide treatment she had mild pedal oedema which resolved with furosemide 40 mgs daily and she continues on this dose of diuretic at present. HbA1c level was 6.1% (43 mmol/mol) prior to diazoxide treatment and 6.6% (49 mmol/mol) recently. The fasting plasma glucose levels in the past 4 years have ranged from 5.4 to 5.9 mmol/l and she remains under surveillance.

Case 3

A 67-year-old man who underwent laparoscopic oesophago-gastrectomy for severe achalasia was referred 2 years after surgery with postprandial palpitations, sweating episodes and abdominal cramps. Symptoms were frequent and could occur soon after meals. A prolonged GTT was not typical of postprandial hypoglycaemia (Table 1) but his home glucose monitoring demonstrated several postprandial readings between 1.7 and 2.4 mmol/l associated with symptoms. He had no improvement with dietary modification. Although there was a marginal benefit with acarbose, he was unable to tolerate it for very long due to nausea and flatulence. He was then commenced on diazoxide and during 6 months of follow-up has had a significant reduction in hypoglycaemia. His most recent HbA1c was 5.6% (38 mmol/mol).

Discussion

We observed a remarkable relief of symptoms in these patients after diazoxide treatment. The first two patients reported complete resolution of their postprandial symptoms and major improvements in their quality of life. The patient described as our third case also had a significant improvement in his symptoms with only occasional mild hypoglycaemia, but so far has been followed only for a relatively short duration. In view of the marked symptomatic improvement, we felt a repeat prolonged GTT was not justifiable on clinical grounds. Cases 1 and 2 presented nearly 30 years after surgery having suffered with these symptoms for many years. It is therefore likely that there are many others living with these symptoms, who remain undiagnosed and untreated or present with symptoms many years after gastric surgery.3

The diagnosis of hypoglycaemic dumping syndrome is based on a history of previous gastric surgery, postprandial symptoms suggestive of hypoglycaemia and demonstration of low blood glucose levels after a glucose load or test meal, or on home glucose monitoring. We used the traditional prolonged GTT to demonstrate hypoglycaemia, though a test meal may be more likely to precipitate hypoglycaemia.4 There are no clear diagnostic criteria for abnormality in the prolonged GTT. However, all our patients had plasma glucose levels below 3.5 mmol/l (≤3 mmol/l in Cases 1 and 2) with hypoglycaemic symptoms during GTT and symptomatic improvement occurred later with diazoxide. The primary event in early dumping is the rapid delivery of hyper-osmolar food into the duodenum which results in a shift of intravascular fluid to the intestinal lumen causing tachycardia, dizziness and abdominal cramps.1 Rapid absorption of glucose and excess incretin hormones particularly glucagon like peptide 1(GLP-1) produced in the ileum enhance insulin secretion resulting in hypoglycaemia in the late dumping phase.5,6 A condition with similar presentation after gastric bypass surgery is hyperinsulinemic pancreatogenous hypoglycaemia which is thought to be secondary to islet cell hyperplasia and nesidioblastosis. Hypoglycaemia in this situation is severe and may respond poorly to medical treatment requiring partial pancreatectomy.7

Dietary modification is the initial step in treating hypoglycaemic dumping syndrome but adherence to diet is poor and benefits are limited. Acarbose can provide modest benefit but is known to cause significant gastrointestinal side effects.8 Octreotide,
particularly the long acting formulation is effective in reducing hypoglycaemia, however the disadvantages are pain related to injections, high costs, steatorrhoea and gall stone formation.\(^9,10\) Diazoxide has not been reported in the treatment of hypoglycaemia after primary gastric surgery but we found it effective in our experience with these three patients.

Diazoxide, a sulphonamide derivative with structural similarity to chlorothiazide was originally synthesized in early 1960s as a non-diuretic antihypertensive agent.\(^11\) In the later years it was used in hypoglycaemic states of diverse aetiology including islet cell tumours and glycogen storage disorders.\(^12\) It is an important therapeutic modality in malignant and metastatic insulinomas where tumours are not localized and surgery is not an option.\(^13\)

Diazoxide activates adenosine triphosphate (ATP) sensitive potassium channels (\(K_{\text{ATP}}\) channel) in the pancreatic \(\beta\) cells. Activated \(K_{\text{ATP}}\) channels increase potassium (K) efflux from the \(\beta\) cells causing it to hyperpolarize. This in turn inactivates voltage-gated calcium channels (VGCC) resulting in inhibition of insulin release.\(^14\) Figure 1. Excess incretin hormones in hypoglycaemic dumping syndrome enhance insulin secretion through a number of mechanisms including inhibition of \(K_{\text{ATP}}\) channels,\(^15\) which is potentially counteracted by diazoxide.

Diazoxide for the treatment of dumping syndrome

**Conflict of interest:** None declared.

**References**


