

POST-GASTRIC-BYPASS HYPOGLYCEMIA SUCCESSFULLY TREATED WITH ALPHA-GLUCOSIDASE INHIBITOR THERAPY

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ABSTRACT

Objective: To review the effectiveness of alpha-glucosidase inhibitor (AGI) therapy in the treatment of hypoglycemia after Roux-en-y gastric surgery.

Methods: Retrospective case review.

Results: Four patients who previously underwent Roux-en-y gastric bypass were evaluated because of severe symptomatic postprandial hypoglycemia that was unresponsive to a low-carbohydrate diet. Mixed-meal testing confirmed hyperinsulinemia. Other causes of hypoglycemia were ruled out by a combination of clinical examination, endocrine testing, and computed tomography imaging. Symptomatic hypoglycemia resolved in all 4 patients after AGI therapy was started. One patient could not tolerate long-term therapy because of a rash. The other 3 patients were followed for between 5 and 48 months and remained free of symptomatic postprandial hypoglycemia.

Conclusion: AGI therapy is effective in the long-term treatment of post-Roux-en-y hypoglycemia in patients unresponsive to a low-carbohydrate diet. To our knowledge, this is the first report documenting the long-term usefulness of this therapy in a series of patients. (*Endocr Pract.* 2013;19:511-514)

Abbreviations:

AGI = alpha-glucosidase inhibitor; GB = gastric bypass

INTRODUCTION

Hypoglycemia after Roux-en-y gastric bypass (GB) surgery was first reported by Service et al (1), who described 6 patients with postprandial hypoglycemia and negative imaging. One patient with multiple, small insulinomas was identified following pancreatectomy. The other 5 patients had various degrees of islet cell hypertrophy and hyperplasia (1). This syndrome, known as noninsulinoma pancreatogenous hypoglycemia (NIPHS), most likely represents a rare cause of GB hypoglycemia. Subsequently, over 80 patients with GB hypoglycemia have been reported, and their clinical presentation has been summarized (2). Unlike the dumping syndrome (3), hypoglycemia in GB patients occurs well after 1 year of the initial surgery (2).

After other causes of hypoglycemia are ruled out, treatment is usually initiated with a low-carbohydrate diet (4). Persistent symptomatic hypoglycemia requires additional therapy. Alpha-glucosidase inhibitor (AGI) therapy limits postprandial hyperglycemia and hyperinsulinemia (5). However, there are only a few reports of the use of AGI therapy in patients with postprandial hypoglycemia unresponsive to low-carbohydrate diet therapy (4,6,7). Below, we characterize the clinical evaluation and AGI treatment of 4 patients presenting with post-GB hypoglycemia, all of whom did not respond to a carbohydrate-restricted diet.

Case 1

A 42-year-old female underwent GB 3 years prior to presenting for evaluation of hypoglycemia. The patient met the criteria of Whipple's triad: neuroglycopenic symptoms 2 to 4 hours after eating foods such as pasta and/or sweet desserts, capillary glucose of 35 to 50 mg/dL, and resolution of symptoms with simple carbohydrates. The patient appeared well and had an unremarkable physical

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examination. Baseline testing ruled out adrenal, thyroid, renal, and hepatic diseases. Mixed-meal testing (8.6 kcal/kg, 50% carbohydrate, 35% fat, and 15% protein) at our endocrine testing unit revealed: fasting blood glucose (BG) level of 83 mg/dL, a 115-minute symptomatic BG level of 42 mg/dL, with simultaneous serum insulin of 14 μ IU/mL (normal, <29.2 μ IU/mL), C-peptide level of 4.2 ng/mL (normal, 0.9 to 6.9 ng/mL), beta-hydroxybutyric acid level of 0.08 mmol/L (normal, 0 to 0.42 mmol/L), and a negative sulfonylurea screen. A computed tomography (CT) scan was negative for a pancreatic mass.

Because the patient's hypoglycemia was exclusively postprandial, empiric therapy was instituted rather than pursuit of a more invasive testing regimen to rule out insulinoma. The patient started a restricted diet including 30 grams of carbohydrate per meal. Although she initially responded to the diet therapy, minimally increasing the carbohydrate intake above 30 grams per meal resulted in symptomatic hypoglycemia. Premeal acarbose at 50 mg three times a day with meals was added, and was titrated to 100 mg as needed. At her 3-year follow-up, the patient indicated having no further symptomatic postprandial hypoglycemia, except when omitting acarbose.

Case 2

A 45-year-old female underwent GB 4 years prior to evaluation for hypoglycemia. Her presentation and testing work-up was similar to case 1. The patient was also placed on a restricted diet including 30 grams of carbohydrate per meal, but her symptoms continued. Acarbose was added to the treatment and the patient remained symptom-free at her 4-year follow-up.

Cases 3 and 4

The remaining 2 cases are summarized in Table 1. Cases 3 and 4 initially failed a carbohydrate-restricted diet

but responded to AGI therapy. About 12 weeks after initiation of AGI treatment, case 4 developed a rash that necessitated discontinuation of the treatment. However, she had an excellent clinical response on therapy. None of the patients were diagnosed with diabetes mellitus prior to GB.

DISCUSSION

The most recent review of symptomatic hypoglycemia in GB patients described an incidence of 0.2 to 6% (2). To date, 89 cases have been reported (Table 2).

A careful history should be elicited to explore fasting versus postprandial hypoglycemia. Documentation of fasting hypoglycemia that satisfies Whipple's triad should prompt an evaluation for insulinoma, glucocorticoid deficiency, hepatic, renal, or thyroid dysfunction, and factitious medication ingestion (8). Our evaluation ruled out most of these etiologies in the cases presented here. Although we did not definitively rule out insulinoma, given the exclusive postprandial symptoms and response to therapy we elected not to perform CT scans on all patients or pursue invasive hepatic vein sampling. Our mixed-meal testing confirmed inappropriate hyperinsulinemia in the presence of symptomatic hypoglycemia.

Symptoms from dumping syndrome can mimic postprandial hypoglycemia. Rapid transit of hyperosmolar contents can lead to nausea, diaphoresis, and hypotension. Hypoglycemia can result from rapid uptake of glucose from the small bowel, with hypoglycemia occurring 45 to 60 minutes after meals (3). Dumping syndrome usually occurs soon after surgery, as opposed to the 1 to 2 year delay in GB patients.

It has yet to be determined why only some GB patients develop symptomatic hypoglycemia. As noted above, a small number of patients are found to have anatomic changes in islet cells that are consistent with NIPHS (1).

Table 1
Summary of Cases 1 through 4

	Case 1	Case 2	Case 3	Case 4
PP BG nadir (65-99 mg/dL) ^a	42	32	56	50
C-peptide (0.9-6.9 ng/mL) ^b	4.2	2.8	Lab error	10.6
Insulin (<29.2 μ IU/mL) ^b	14.4	16.4	Lab error	46.7
CT abdomen	Negative	Not done	Not done	Negative
Treatment	Carb-restricted diet & acarbose	Carb-restricted diet & acarbose	Carb-restricted diet & acarbose	Carb-restricted diet, allergic to acarbose and miglitol
Abbreviations: BG = blood glucose; PP = postprandial. ^a Following mixed meal; all patients symptomatic. ^b C-peptide and insulin levels obtained simultaneously with BG.				

Report	Cases (no.)	Mean age (years)	Time of onset after GB (months)	Lowest glucose level (mg/dL)
Ritz et al (2)	89	44	28.6	41.4 (at time of symptoms)
Current series	4	43	42	37 (mixed meal nadir)
Abbreviation: GB = gastric bypass.				

However, Meier et al (9) did not find islet cell hypertrophy or hyperplasia. A generalized increase in beta-cell mass secondary to obesity has also been postulated to contribute to GB hypoglycemia with maladaptation after weight loss. A decrease in the apoptosis of beta-cells in these obese GB patients could contribute to hyperinsulinemia. This theory may not be correct, as it has been pointed out that severe hypoglycemia does not occur with weight loss in obese patients who undergo restrictive (i.e., gastric banding) procedures (10). Attention has also been focused on exaggerated secretion of incretins after meal ingestion. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide levels were found to be significantly higher in GB patients with symptomatic hypoglycemia than in asymptomatic GB patients (11). These incretins can increase beta-cell mass, at least in animal models (10). Although hard data are lacking, it is possible that alterations in the levels of other hormones, such as ghrelin, peptide YY, gastric inhibitory peptide, glucagon, and perhaps an as yet uncharacterized hormone could potentially play a role in post-bypass hypoglycemia. A comprehensive review of all of the pathophysiologic mechanisms that may be involved is beyond the scope of this paper, but can be found elsewhere (10).

Low-carbohydrate diet therapy is usually the first step instituted to treat symptomatic GB hypoglycemia. Kellogg et al (4) described 12 GB patients with symptomatic hypoglycemia that was treated with a diet of very low carbohydrate content. Complete or partial improvement of symptoms was seen in 10 of the 12 patients.

Moreira (7) first described the use of the calcium-channel blocker verapamil to treat a patient with GB-associated hypoglycemia. After initial improvement on verapamil 80 mg twice daily, recurrent hypoglycemia was treated with the addition of acarbose. Diazoxide has been used to treat hypoglycemia from dumping syndrome, but has not been reported in the treatment of GB hypoglycemia (12). Somatostatin therapy has been suggested, but has not been extensively studied (13).

There are various reports on patient responses to AGI therapy. Acarbose has been shown to decrease postprandial hyperglycemia after mixed-meal testing, as well as attenuate the rise in insulin and GLP-1 levels (5). Kellogg et al (4) noted that 2 patients were placed on acarbose after failing low-carbohydrate diet therapy, with 1 patient experiencing improvement. Hanaire et al (6) also described the use of acarbose in a single patient with post-bypass hypoglycemia. Home monitoring showed hypoglycemia after intake of high-glycemic index foods. The 8-month follow-up revealed that avoidance of such foods in addition to acarbose prevented symptomatic hypoglycemia.

CONCLUSION

Cases 1 and 2 highlight the long-term response (over 3 to 4 years) to AGI therapy. Case 3 remained markedly improved after 4 months of therapy. Case 4 also had a significant decrease in the frequency and severity of hypoglycemia, but development of a rash required discontinuation of AGI therapy. We suggest that AGI therapy can be used for long-term treatment of GB patients who experience hypoglycemia and who fail low-carbohydrate diet therapy.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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