Successful Treatment of Reactive Hypoglycemia Secondary to Late Dumping Syndrome Using Miglitol

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Abstract

We herein describe a 59-year-old woman who had undergone a total gastrectomy for gastric carcinoma and suffered from postprandial hypoglycemia characterized by a loss of consciousness and spasms. She was diagnosed with reactive hypoglycemia and treated with nutrition therapy, but the frequency and severity of the hypoglycemic episodes did not decrease. She was subsequently treated successfully with miglitol, an alpha-glucosidase inhibitor (α-GI) taken twice a day; other α-GIs (acarbose and voglibose) were not effective. In conclusion, the administration of miglitol was effective for preventing reactive hypoglycemia secondary to late dumping syndrome.

Key words: reactive hypoglycemia, dumping syndrome, alpha-glucosidase inhibitor

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Introduction

Reactive hypoglycemia is defined as a clinical disorder in which hypoglycemic symptoms occur postprandially. Serious and life-threatening hypoglycemia can occur without appropriate treatment (1, 2). Reactive hypoglycemia can be caused by fructose intolerance, galactosemia, drugs, and late dumping syndrome (3, 4). Late dumping syndrome is seen in 10-40% of patients after gastric surgery (5) and in more than 50% of patients after esophagectomy (6). In Japan, gastric cancer is one of the leading causes of cancer deaths (7), and gastrectomy is the mainstay of curative treatment (8).

Patients with reactive hypoglycemia secondary to late dumping syndrome are treated via dietary modifications, wherein meals are eaten five or six times a day, and the carbohydrate intake is reduced. However, this nutrition therapy is not always successful at preventing the development of hypoglycemia.

Alpha-glucosidase inhibitors (α-GIs), which are oral antidiabetic agents, work primarily in the small intestine. Because they reduce carbohydrate metabolism and carbohydrate absorption, they modulate the postprandial increase in the plasma glucose and insulin levels. Acarbose, an α-GI, has been reported to be effective in idiopathic reactive hypoglycemia (9, 10) and in late dumping syndrome (11, 12).

We herein report the case of a woman who suffered from severe reactive hypoglycemia secondary to late dumping syndrome and was successfully treated with miglitol twice a day, but for whom acarbose and voglibose were ineffective.

Case Report

A 59-year-old woman was admitted to Osaka University Hospital in September 2011 for the assessment and treatment of postprandial hypoglycemia. She had undergone total gastrectomy for gastric carcinoma in 2003. At that time, she was instructed to eat 6 divided small meals in a day, but she...
frequently suffered from hypoglycemic episodes characterized by a loss of consciousness and spasms that occurred a few hours after meals. On two occasions, she was taken to an emergency room for hypoglycemic episodes; her plasma glucose level was 89 mg/dL. Her fasting plasma glucose (FPG) level was 89 mg/dL. Her fasting immunoreactive insulin (F-IRI) and C-peptide immunoreactivity (F-CPR) were 1.9 μU/mL and 1.2 ng/mL, respectively. She was positive for anti-glutamic acid decarboxylase (GAD) antibodies. Although the anti-thyroglobulin antibody (TgAb) titer was also positive, her thyroid function was almost normal. Her adrenal function was also normal (Table).

An abdominal computed tomography (CT) scan detected no abnormalities in the pancreas. In a 75 g oral glucose tolerance test (OGTT), the baseline glucose and IRI levels were 95 mg/dL and 2.9 μU/mL, respectively; they rapidly increased to 378 mg/dL and 267.2 μU/mL after 60 minutes and decreased to 41 mg/dL and 5.9 μU/mL after 150 minutes (Fig. 1). Continuous glucose monitoring (CGMS-Gold™, Medtronic Minimed, Northridge, CA) under her regular diet revealed the mean blood glucose level to be 108 ± 52 mg/dL, and the blood glucose levels rapidly increased postprandially and then decreased to hypoglycemic levels after breakfast (Fig. 2A).

On the basis of these results, her hypoglycemia was diagnosed as reactive hypoglycemia secondary to late dumping syndrome. Every meal was divided into two, and the second meal was eaten 2 hours after the first. The total energy of the meals was 1,520 kcal/day. With the smaller, more frequent meals, the daily fluctuations in the blood glucose levels were reduced, and the mean blood glucose level was 108 ± 35 mg/dL. However, the reactive hypoglycemia following breakfast could not be prevented by dietary modifications alone (Fig. 2B). She was therefore given an additional α-GI orally, in combination with the dietary modifications. Because the postprandial hyperglycemia and hypoglycemia were most pronounced after breakfast in the hospital, an α-GI was administered once in the morning before the first
meal. With the smaller, divided meals in combination with 0.3 mg of voglibose or 100 mg of acarbose, the mean blood glucose levels were 100 ± 40 mg/dL and 104 ± 37 mg/dL, respectively. Hence, these α-GIs were not effective for reducing the fluctuations of the blood glucose levels (Fig. 2C, D). However, after administration of 50 mg of miglitol, the mean blood glucose level was 92 ± 11 mg/dL, and the fluctuations throughout the day were markedly reduced (Fig. 2E).

The profiles of the blood glucose and IRI levels after breakfast (Fig. 3A, B) and after lunch (Fig. 3C, D) with the dietary modifications showed postprandial hyperglycemia and hyperinsulinemia, especially after breakfast. The administration of 0.3 mg of voglibose slightly reduced postprandial hyperinsulinemia following breakfast, but had no effect on the postprandial hyperglycemia after either breakfast or lunch. However, the administration of 50 mg of miglitol ameliorated both the postprandial hyperglycemia and the hyperinsulinemia, and the blood glucose level was elevated 120 minutes after breakfast, when reactive hypoglycemia often occurred.

Under a regimen of 50 mg of miglitol once a day, the peak plasma concentration (Cmax) of miglitol was 2.2 μg/mL, the peak time (tmax) was 2.0 hours, and the half-life (t1/2) was 2.8 hours. The amount of miglitol excreted in the urine was 28.5 mg/day, corresponding to 57% of the daily dose.

Under a regimen of 50 mg of miglitol once in the morning, the patient had infrequent hypoglycemic episodes after dinner in the hospital. Therefore, she was given an additional 50 mg of miglitol in the evening. After discharge, she was often constipated and was admitted to another hospital for a bowel obstruction, which was managed conservatively. Because her hypoglycemia is life-threatening, she has been carefully treated with the same dose of miglitol in conjunction with a laxative, and during the more than 6 months of follow-up, has not experienced any hypoglycemic episodes.

**Discussion**

We determined that miglitol, administered at 50 mg twice a day, was effective for preventing reactive hypoglycemia secondary to late dumping syndrome, and the efficacy of this agent was superior to that of two other α-GIs, voglibose and acarbose. The differences in efficacy between these α-GIs might be attributable to their respective pharmacodynamics and pharmacokinetic properties. First, miglitol inhibits α-glucosidase in the upper section of the small intestine, which is the main site of intestinal absorption of glucose; almost all the miglitol is absorbed at this site (13, 14). In contrast, voglibose...
and acarbose are not absorbed, and thus inhibit α-glucosidase throughout the small intestine. Second, miglitol has different specificities and affinities for the various metabolic enzymes compared with voglibose and acarbose (15). While acarbose is a complex oligosaccharide, miglitol is structurally similar to glucose; this similarity is suggested to be related to its broader specificity of inhibition against α-glucosidases (13). The inhibition of α-glucosidase primarily in the upper section of the small intestine and the broader specificity may lead to a significant advantage for miglitol in reducing the rapid postprandial increase of blood glucose and IRI levels compared with other α-GIs in patients with reactive hypoglycemia secondary to dumping syndrome, as has been reported in patients with type 2 diabetes (16-18).

The saturated absorption of miglitol in the upper section of the small intestine may be one mechanism through which the twice-daily administration of 50 mg of miglitol could prevent postprandial hyperglycemia and the reactive hypoglycemia throughout the day. At this site, the absorption of miglitol is already saturated, as has been reported for Caucasians, within the therapeutic dose range (with doses ≥50 mg or ≥0.7 mg/kg), and miglitol is not readily absorbed in the ileum or colon (14). For our patient, the administration 50 mg of miglitol corresponded to 1.1 mg/kg of miglitol. The unabsorbed miglitol may inhibit α-glucosidase for a longer period of time in the lower sections of the small intestine or colon. Indeed, when she was administered 50 mg of miglitol once a day, the daily amount of excretion of miglitol via urine corresponded to approximately 60% of the daily dose, thus suggesting that 40% could not be absorbed.

Another possible mechanism may be related to a change in incretin secretion. Miglitol enhances postprandial secretion of glucagon-like peptide-1 (GLP-1) (19-24), a gut peptide secreted by intestinal L cells in response to nutrient ingestion. In addition, the administration of miglitol once in the morning induced a prolonged increase of GLP-1 secretion not only after breakfast, but also after lunch, in non-diabetic men (19) and in patients treated with sitagliptin for type 2 diabetes (20). GLP-1 has a physiological effect of inhibiting gastrointestinal motility, including the slowing of gastric emptying (25, 26). An increased release of GLP-1 following the administration of miglitol may cause a decrease in gastrointestinal motility. In our patient who had undergone a total gastrectomy, the decreased gastrointestinal motility other than gastric emptying might have led to a reduction in the rapid postprandial increase in the glucose and insulin levels, which are the main causes of reactive hypoglycemia secondary to late dumping syndrome. In this case, the C_{max} of miglitol was much higher, and the t_{1/2} was slightly longer than that in healthy volunteers who were ad-

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**Figure 3.** The profiles of the blood glucose and IRI levels (A, B) after breakfast and (C, D) after lunch with divided meals (○), after the addition of 0.3 mg of voglibose (■) or after the addition of 50 mg of miglitol (X).
ministered 1.4 mg/kg of miglitol (C<sub>max</sub>: 1.13 μg/mL, t<sub>1/2</sub>: 2.35 hours), while the duration of time at the t<sub>max</sub> was not longer (2.0 hours in this case v.s. 2.3 hours in healthy volunteers) (14). It has been speculated that gastric surgery may induce augmented GLP-1 secretion and retention of miglitol in the upper section of the small intestine, while the absence of the stomach may allow miglitol to more rapidly reach the upper section of small intestine, thus leading to almost the same t<sub>max</sub>. Therefore, the increased and prolonged release of GLP-1 resulting from twice-daily administration of miglitol may have contributed to the prevention of reactive hypoglycemia throughout the day. However, the secretion of miglitol-induced incretin, in addition to abdominal surgery, may reduce gastrointestinal motility and thus lead to bowel obstruction, as occurred in this case. The blood incretin concentations and the rate of gastrointestinal motility were not examined in this patient. Therefore, further studies are needed to investigate this hypothesis.

In conclusion, the administration of miglitol, but not other α-GIs, twice a day was effective for preventing reactive hypoglycemia secondary to late dumping syndrome in our patient.

The authors state that they have no Conflict of Interest (COI).

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References


