Combined Dipeptidyl Peptidase 4 Inhibitor and α-Glucosidase Inhibitor Treatment in Postprandial Hypoglycemia

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Background

Postprandial, or reactive, hypoglycemia (RH) is an uncommon condition in which patients develop signs and symptoms of hypoglycemia within 2–5 hours after a meal. RH is clinically seen in three different forms: idiopathic RH (at 180 minutes), alimentary RH (within 120 minutes), and late RH (at 240–300 minutes) (1). The diagnosis is made when neuroglycopenic symptoms consistent with hypoglycemia are present in association with a low plasma glucose concentration <55 mg/dL [2.8 mmol/L] measured with a precise method, and the symptoms are relieved after the plasma glucose level increases (1,2).

Frequent small meals or snacks (every 3 hours) with a diet high in fiber, avoidance of foods high in sugar, and a regular exercise regimen have been recommended (3,4). When lifestyle interventions are unsuccessful, a trial of α-glucosidase inhibitor treatment is recommended to delay carbohydrate absorption and reduce the insulin response to meals (5–8). Recently, there have been reports of the use of dipeptidyl peptidase 4 (DPP-4) inhibitors for postprandial hypoglycemia (1,9), but never in combination with α-glucosidase inhibitor treatment.

We present a case of novel use of combination treatment with a DPP-4 inhibitor and an α-glucosidase inhibitor for idiopathic postprandial RH that was refractory to lifestyle intervention and α-glucosidase inhibitor treatment alone.

Case Presentation

A 24-year-old Caucasian woman with a medical history significant for generalized anxiety disorder, major depressive disorder, borderline personality disorder, restrictive eating disorder, psychogenic non-epileptiform seizures, postural orthostatic tachycardia syndrome, and carcinoid tumor of the appendix (surgically removed with appendectomy) presented to the emergency department after experiencing 2 days of neck pain and frontal headache. She developed seizure-like activity in the waiting room. Her point-of-care (fingerstick) blood glucose was 81 mg/dL in the emergency department. She was afebrile, with a blood pressure of 90/61 mmHg, respiratory rate of 18 breaths/min, and BMI of 23.82 kg/m^2. Physical examination demonstrated an emotionally distraught young woman with no other significant findings.

Two years before this presentation, she had a 5-hour, 75-g oral glucose tolerance test (OGTT) without evidence of impaired fasting glucose (IFG) and development of a nadir glucose level of 44 mg/dL at 180 minutes. This OGTT result was consistent with idiopathic postprandial RH (Table 1). ACTH stimulation testing demonstrated an adequate response, and her A1C was 4.6%. After testing, she had been started on lifestyle interventions (a diet high in fiber and avoidance of foods high in sugar), and acarbose 25 mg three times daily given 30 minutes before meals. Despite lifestyle interventions and acarbose, plus a 3-month trial of metformin, she still developed symptomatic hypoglycemic episodes 2–3 hours after meals.

During this hospital stay, she was admitted from the emergency department for further neurological assessment and a supervised 72-hour fast. After 43 hours, she had a fingerstick plasma glucose of 49 mg/dL (reference 74–99 mg/dL), with a corresponding plasma glucose draw of 56 mg/dL (reference 74–99 mg/dL), β-hydroxybutyrate of 3.08 mmol/L (reference <0.28 mmol/L), C-peptide of 0.4 ng/mL (reference 0.5–2.7

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https://doi.org/10.2337/cd21-0042

TABLE 1 5-Hour OGTT Results

Time	Point-of-Care Glucose, mg/dL	Plasma Glucose, mg/dL	Insulin, μU/mL	C-Peptide, ng/mL	β-Hydroxybutyrate, mmol/L
Baseline	77	71	6.2	1.2	0.18
30 minutes	111	105	89.4	7.7	–
60 minutes	81	72	78.5	9.4	–
90 minutes	89	83	61.5	8.2	–
120 minutes	81	70	29.7	4.6	–
180 minutes	**56**	**44**	**4.6**	**2.2**	–
210 minutes	73	–	–	–	–
240 minutes	81	73	3.8	1.1	–
300 minutes	85	78	5.5	0.9	–

Bold type at 180 minutes represents the time point at which the patient developed symptomatic hypoglycemia.

ng/mL), proinsulin <1.6 pmol/mL (reference <22 pmol/mL), and insulin <0.5 μU/mL (reference <25 μU/mL), with a negative screen for sulfonylurea and meglitinide.

Further neurological workup failed to demonstrate seizure activity during her inpatient stay, and it was determined that her seizure-like activity was from psychogenic non-epileptiform seizures. When a high-fiber, high-protein, carbohydrate-controlled (45–75 g/meal) diet was initiated with an α-glucosidase inhibitor (acarbose) at 25 mg three times daily given 30 minutes before meals, she continued to have postprandial hypoglycemic episodes 2–3 hours after meals to a nadir of 38 mg/dL. After 2 days of RH, a 5% dextrose 0.9% sodium chloride (NaCl) infusion was started at 125 mL/hour, which was later transitioned to 10% dextrose 0.9% NaCl at 100 mL/hour. A single dose of 50 μg subcutaneous octreotide was given on hospital day 7 without improvement, and her 10% dextrose 0.9% NaCl infusion was increased to 125 mL/hour on hospital day 8. On day 9, the acarbose was increased to 100 mg three times per day given 30 minutes before meals, but she continued to develop recurrent RH episodes. On day 13, DPP-4 inhibitor treatment (sitagliptin) 100 mg daily was added, and she was weaned off of the 10% dextrose 0.9% NaCl infusion over the next 48 hours (days 12–14). Throughout the remainder of her inpatient stay (hospital days 14–19), she did not develop further episodes of hypoglycemia, with fingerstick glucose readings in the range of 70–125 mg/dL.

Questions

1. What is known regarding the treatment of idiopathic postprandial hypoglycemia (also called RH)?
2. What is the proposed mechanism of action of combining treatment with a DPP-4 inhibitor and an α-glucosidase inhibitor for RH?

Commentary

RH is often treated with frequent small meals and snacks (every 3 hours), consisting of foods that are high in fiber and low in sugar, along with regular exercise (3,4). RH is clinically seen in three different forms: idiopathic RH (at 180 minutes), alimentary RH (within 120 minutes), and late RH (at 240–300 minutes) (1). If lifestyle intervention is not successful in reducing symptoms in idiopathic RH, then an α-glucosidase inhibitor is used to delay carbohydrate absorption and thereby reduce insulin response to meals (1,5–7). In a double-blind study, acarbose significantly reduced the magnitude of post-sucrose RH (7). In a separate acute, double-blind, cross-over study, miglitol significantly blunted the post-load rise in plasma glucose, with a significant improvement in the hypoglycemic index, as well as a significant dampening of plasma insulin and C-peptide secretion. This study also showed that there was a significant decrease in plasma gastric inhibitory polypeptide (GIP) peak and total area under the GIP curve. It is therefore believed that α-glucosidase treatment blunts the insulin response to glucose directly by delaying glucose absorption and indirectly by reducing GIP secretion (8).

DPP-4 inhibitors are known to increase early insulin response and reduce circulating glucagon levels during an OGTT and mixed-meal tolerance test (MTT), respectively (1,9). These effects are known to be glucose dependent and minimize both hyper- and hypoglycemia (1). A double-blind, parallel-group study of Japanese patients with impaired glucose tolerance treated for 7–8 weeks with sitagliptin significantly reduced glucose excursions during both an MTT and an OGTT. The effect was associated with an increase in early insulin secretion after oral glucose loading, as well as a blunted glucagon response during an MTT (9). Sitagliptin was recently evaluated in a randomized, double-blind, placebo-controlled clinical trial, in which it was found to improve first-phase insulin secretion and reduce postprandial hypoglycemia (10). Lastly, it was demonstrated that DPP-4 inhibitors do not lower postprandial glucose concentrations by altering the rate of nutrient absorption or delivery to systemic circulation. DPP-4 inhibitors alter islet cell function by increasing circulating concentrations of active glucagon-like peptide 1 (GLP-1) and are associated with a decrease in postprandial glycemic excursion (11).

Metformin and α-glucosidase inhibitor therapy may be recommended if there is late RH (in the third to fifth hour of an OGTT) with IFG (1). Additionally, GLP-1 receptor agonists are believed to have a preventive effect on postprandial RH with prediabetes or in overweight patients (1,10,12–14) but have not been studied in patients without IFG or patients who are not overweight or obese. With GLP-1 receptor agonists, there is an association with marked improvement in glucose tolerance and reversion of prediabetes to normal glucose tolerance in >50% of patients (1,10,12–14). Although the mechanism of action of both α-glucosidase inhibitors and DPP-4 inhibitors are understood in isolation, the use of these agents in combination is not.

α-Glucosidase inhibitors (acarbose and miglitol) reduce levels of both GIP and glucagon (15), delay glucose absorption, and thereby blunt the insulin response to glucose (16). DPP-4 inhibitors are known to increase the early insulin response (by increasing circulating concentrations of active GLP-1), reduce glucagon secretion in a glucose-dependent manner, and therefore reduce both hyper- and hypoglycemia. We believe that, through different mechanisms of action, α-glucosidase inhibitors and DPP-4 inhibitors can be combined to reduce GIP and glucagon and more appropriately match glucose-dependent early insulin release. Although the combination of these two drugs has been suggested to provide an additive (or perhaps synergistic) effect on glucose control with complementary mechanisms of action in patients with type 2 diabetes (17), this is the first case that demonstrates additive utility in postprandial RH. This patient's clinical case demonstrates the utility of combining an α-glucosidase inhibitor with a DPP-4 inhibitor in refractory idiopathic postprandial RH.

Clinical Pearls

- RH is an uncommon condition in which patients develop hypoglycemia within 2–5 hours after a meal.
- There are three different clinical forms of RH: idiopathic (within 180 minutes), alimentary (within 120 minutes), and late (240–300 minutes).
- Lifestyle interventions, including frequent small meals (every 3 hours) that are high in fiber and low in sugar and regular exercise, are the mainstays of treatment.
- α-Glucosidase inhibitor treatment is effective for RH if lifestyle intervention fails to prevent it.
- DPP-4 inhibitor treatment is effective for RH in patients both with and without IFG.
- If a diet high in fiber and low in sugar and α-glucosidase inhibitor treatment fail to prevent RH, adding a DPP-4 inhibitor is effective.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

D.T.B. wrote the manuscript. All other authors edited and revised the manuscript. R.S.Z. is the guarantor of this work and takes responsibility for the integrity of the case study.

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