Quetiapine-Induced Severe Hypoglycemia in Patient Without Diabetes Mellitus: A Case Report

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Received: December 12, 2018

Revised: February 1, 2019

Accepted: February 10, 2019

Hypoglycemia is a serious event in older patients with diabetes mellitus because it increases the risk of various conditions including cardiovascular disease, and dementia, as well as the risk of falls in these individuals. Quetiapine is a widely used antipsychotic drug with diverse indications, and it may be prescribed to older patients. We report on our treatment of an older individual without diabetes mellitus who manifested severe hypoglycemia induced by quetiapine. The hypoglycemia was accompanied by endogenous hyperinsulinemia but was not related to the presence of a pancreatic tumor or antibodies, and adrenal function was normal. The hypoglycemia was so severe that only massive 20% dextrose infusion could maintain normoglycemia. After the patient stopped taking quetiapine, his blood glucose concentration started to increase slowly toward normoglycemia. We finally diagnosed this case as quetiapine-related severe hypoglycemia in a patient without diabetes mellitus, and report our findings here. (*Ann Geriatr Med Res* 2019;23:35-37)

Key Words: Hypoglycemia, Aged, Quetiapine fumarate

INTRODUCTION

Hypoglycemia is a serious medical condition and one of the most important medical issues in patients with diabetes, because it is primarily caused by antidiabetic medications. Hypoglycemia can contribute to or cause injuries, dementia, cardiovascular events, arrhythmias, coma, and death.¹⁾

Quetiapine is used widely for the treatment of schizophrenic or other psychotic symptoms. Older individuals are often treated with quetiapine to relieve psychotic symptoms associated with conditions including dementia and delirium.²⁾ Hyperglycemia is an adverse event frequently observed in individuals without diabetes who receive quetiapine, and thus patients are monitored for these hyperglycemic episodes with 75-g oral glucose tolerance tests (OGTT). However, blood glucose concentration reductions to 47–53 mg/dL are rarely detected by a 75-g OGTT, although such cases have been reported.³⁻⁷⁾ Quetiapine is known to be able to induce mild hypoglycemia in patients without diabetes. We report on our experience treating an older individual without diabetes who developed severe hypoglycemia as a result of administration of quetiapine.

CASE REPORT

A 74-year-old man was admitted to our emergency department with abdominal pain that had begun 1 day before presentation. He complained of yellowish watery diarrhea, abdominal pain, and diaphoresis. His medical history was significant for a cerebrovascular accident (CVA), heart failure, and vascular dementia. His only prior surgeries were vertebral fixation and a cataract operation. The patient had begun to take rosuvastatin, donepezil, clopidogrel, cilostazol, and quetiapine for vascular dementia after the CVA. Along with these medications, he also took candesartan, furosemide, and carvedilol for heart failure. At the time of admission, the patient's dose of quetiapine had been increased gradually from 50 mg to 300 mg a day over the preceding 2 months. The dose had been changed to 300 mg 1 week prior to admission. The patient's family confirmed that he had not consumed alcohol for the past 3 years.

The patient's initial vital signs were blood pressure 96/64 mmHg, heart rate 68/min, and body temperature 36.6°C. He showed only mild periumbilical tenderness on physical examination. Initial laboratory results indicated hypoglycemia (34 mg/dL), hypokalemia (3.2 mmol/L), and elevated creatinine level (1.92 mg/dL) with a normal blood urea nitrogen (17.1 mg/dL). Other laboratory data showed

significant changes including mildly elevated white blood cell count ($11,000/\text{mm}^3$) and normal levels of aspartate aminotransferase and alanine aminotransferase, sodium, chloride, and C-reactive protein. Abdominal computed tomography (CT) showed no abnormal results related to his abdominal pain. Therefore, our clinical impression was that the patient's abdominal pain and diarrhea were caused by enteritis, and we treated him with ciprofloxacin and hydration.

The patient exhibited sustained hypoglycemia (blood glucose concentration $< 40 \text{ mg/dL}$) for 48 h after admission, with amelioration of the diarrhea (Fig. 1). Because he was consuming an insufficient amount of food (diet 2,200 kcal), the patient was administered peripheral intravenous nutritional support (glucose 225 g, triglyceride 37.5 g, and various amino acids). A rapid adrenocorticotrophic hormone test showed a normal response with peak cortisol level of $22.5 \text{ } \mu\text{g/dL}$, and we excluded adrenal insufficiency as a cause of hypoglycemia. The other results were glucose 42 mg/dL , serum C-peptide 19.17 ng/mL , insulin $66.92 \text{ } \mu\text{U/mL}$, and hemoglobin A1c level 5.7%. These results suggested that the cause of hypoglycemia was endogenous hyperinsulinemia. However, CT scans showed no masses in the pancreas or other organs.

The patient in this report usually runs and walks for 2 h after rising each morning prior to eating anything and had never previously experienced hypoglycemic symptoms. The mentioned blood test and CT scan results indicated that his hypoglycemia was not caused by insulinoma or nesidioblastosis, the main causes of endogenous hyperinsulinemia. We also excluded autoimmune hypoglycemia because the test results were negative for anti-insulin antibody and anti-insulin receptor antibody. This patient's hypoglycemia was very severe, and his blood glucose level remained $< 50 \text{ mg/dL}$ even with administration of 10% dextrose at 160 mL/h . We therefore decided to infuse a higher concentration of glucose via a peripherally inserted central catheter. We also treated the patient with gluco-

corticoid 300 mg per day via continuous infusion, but this had no effect on his hypoglycemia. The patient's blood glucose level was maintained at $> 100 \text{ mg/dL}$ after infusion of 20% dextrose 100 mL/h .

Finally, we attempted to exclude drugs as a cause of hypoglycemia, and decided to sequentially eliminate drugs with a high potential for hypoglycemia. We first stopped ciprofloxacin and then quetiapine 24 h later (although we noted that quetiapine is rarely a cause of hypoglycemia). Following termination of quetiapine, the patient's blood glucose level started to increase, and we were able to decrease the rate and concentration of dextrose fluid and eventually stop this infusion. Laboratory data showed levels of C-peptide 1.1 ng/mL , insulin $6.9 \text{ } \mu\text{U/mL}$, and blood glucose 84 mg/dL on the day prior to the patient's discharge, and he was discharged without any complications. The patient has experienced no symptoms related to hypoglycemia in the past 6 months.

DISCUSSION

The population is aging worldwide, and the prevalence rates of several diseases, including cerebrovascular disease, dementia, cardiovascular disease, Parkinson's disease, and diabetes mellitus, are increasing in the older population. Korea and Japan have the highest percentages of older individuals worldwide.⁸⁾ Quetiapine is widely used to relieve psychotic symptoms in older patients with various conditions. Quetiapine can induce hyperglycemia as a minor adverse event, and mild hypoglycemia is a rare adverse event that is usually without symptoms. Previous reports show that quetiapine can induce mild hypoglycemia and that most cases are detected accidentally when the patient is examined for hyperglycemia.³⁻⁷⁾

In the present case, quetiapine-induced hypoglycemia was more severe than that described in previous reports, and was sufficiently severe to require a massive 20% dextrose fluid infusion. Quetiapine, a second generation antipsychotic drug, has an high affinity for and an antagonistic effect on the histamine H1, adrenergic α_1 , muscarinic M1, 5-HT_{2A}, 5-HT₇, dopamine D₂, and D₃ receptors.⁹⁾ Second generation antipsychotic drugs exert their effects through these various receptors. By interacting with these receptors, quetiapine may increase the amount of basal insulin secreted by pancreatic β -cells and thereby cause hypoglycemia.¹⁰⁾ Insulin is secreted by pancreatic β -cells independent of other types of hormone-secreting cells, which together with β -cells form the islets of Langerhans.¹⁰⁾ Quetiapine is an antagonist of muscarinic receptors and may influence the action of insulin through its effects on these receptors; this is another possible mechanism to explain quetiapine-related hypoglycemia.⁹⁾ However, the mechanism underlying quetiapine-induced hypoglycemia remains unclear, and further studies are required.

The present case demonstrates that quetiapine can be a cause of severe hypoglycemia in older individuals, even

Fig. 1. Change in blood sugar levels according to clinical course.

those without diabetes. Since quetiapine is used for the relief of psychotic symptoms, it is crucial to understand the potential adverse effects related to the use of this medication, and to observe any symptoms that may appear. One case report described blonanserin as another option for improving hypoglycemia related to quetiapine use.⁵⁾ We suggest that clinicians should carefully observe older patients receiving quetiapine to identify any hypoglycemic symptoms that may appear. If the etiology of hypoglycemia is not clear in patients using quetiapine, it is important to consider quetiapine as a possible cause.

CONFLICTS OF INTEREST DISCLOSURES

The researchers claim no conflicts of interest.

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