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Second-Generation Antipsychotic–Induced Hypoglycemia

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ABSTRACT

Complaints of hypoglycemia resemble the sedative effect of antipsychotics. As such, clinicians may overlook hypoglycemia in patients with psychiatric disorders. Here, a case of hypoglycemia associated with hyperinsulinemia induced by quetiapine in a female patient with bipolar disorder is reported. The case suggests that clinicians should be aware of the potential for hypoglycemia induced by second-generation antipsychotics.

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Quetiapine, a second-generation antipsychotic (SGA), is regularly prescribed for the treatment of psychotic and mood disorders. Quetiapine use is associated with various metabolic side effects, including obesity and diabetes.[1–4] SGAs increase risk for type 2 diabetes mellitus, and the proposed mechanism for this development centers on drug-induced weight gain. This mechanism initiates the dysmetabolic cascade of insulin resistance, increases insulin production, and causes pancreatic β cell failure. In SGA-treated patients with drug-induced weight gain, metabolic syndrome, or prediabetes, fasting hyperinsulinemia has been identified as a biomarker of insulin resistance.[3,4] Conversely, few reports[5–12] have shown treatment with SGAs to be associated with hypoglycemia. Complaints of hypoglycemia resemble the sedative effect of SGAs. As such, clinicians may overlook hypoglycemia in patients with psychiatric disorders. Hypoglycemia can cause seizures, permanent neurologic damage, or death and can also generate symptoms of adrenergic stimulation, such as irritability and anxiety. Recurrent hypoglycemia may lead to cognitive impairment and the onset of dementia.[13]

We report a case of hypoglycemia associated with hyperinsulinemia induced by quetiapine in a female patient with bipolar disorder. Relevant literature is also reviewed.

CASE REPORT

Ms A is a 62-year-old woman with no personal history of psychiatric or physical illness, including diabetes mellitus. Her family history includes a younger sister with major depressive disorder. She presented to the psychiatry clinic of a university hospital with psychiatric symptoms, including depressed mood, insomnia, appetite loss, and loss of motivation. She began to experience these symptoms at age 61 years and soon became unable to do housework. Initially, dementia was suspected, but neuroimaging and neurocognitive examination revealed no definite abnormalities. She was diagnosed with major depressive disorder (*DSM-5* criteria), and duloxetine was prescribed. However, she began to complain of constipation and diarrhea. No definite abnormalities were observed during the gastrointestinal examination. However, appetite loss led to extreme emaciation, and she became unable to walk. She was subsequently admitted to the hospital.

Ms A's fasting blood sugar level at admission was 85 mg/dL. She was initially prescribed mirtazapine 15 mg/day for her depressive symptoms. Her body mass index at admission was 11.8, but she refused to eat. Delirium soon emerged, most likely due to undernutrition, and tube feeding and quetiapine 25 mg/day were started. Laboratory data revealed hypoglycemia with no clinical symptoms immediately after prescription of quetiapine. Therefore, quetiapine was discontinued, and risperidone 0.5 mg/day was prescribed. The patient's hypoglycemia gradually ameliorated. After 1 month, she began to eat, and tube feeding was stopped. After another month, she

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Clinical Points

- Complaints of hypoglycemia resemble the sedative effects of antipsychotics.
- Clinicians should be aware of the potential for hypoglycemia induced by second-generation antipsychotics.

began to show hypomanic symptoms, such as talkativeness, mood elevation, grandiosity, and delusions of grandeur. Ms A was diagnosed with bipolar disorder (*DSM-5* criteria), and, thus, mirtazapine 15 mg/day was stopped. Lithium 400 mg/day was effective in treating her mood and psychiatric symptoms, which gradually ameliorated within 4 months. Since discontinuation of quetiapine, hypoglycemia has not been observed for a year and 6 months.

DISCUSSION

Hypoglycemia observed in the present case appeared immediately after the prescription of quetiapine and disappeared after the switch from quetiapine to risperidone. Therefore, quetiapine seemed to be the cause of hypoglycemia in Ms A. As shown in Table 1, an oral glucose tolerance test (OGTT) revealed remarkable hyperinsulinemia during the administration of quetiapine but not risperidone. Hyperinsulinemia thus seemed to cause persistent hypoglycemia during the administration of quetiapine. The patient's HOMA-IR[14] (Homeostatic Model Assessment-insulin resistance) score remained below 4, indicating no insulin resistance. It has been reported that hyperinsulinemia can lead to an increased and more rapid feeling of satiety in anorexia nervosa and depression.[13] Increased suppression of serum ghrelin concentration by hyperinsulinemia in women with anorexia has also been reported.[15] These results may account for severe appetite loss during the administration of quetiapine. A decreased level of HOMA-β may be attributable to a low nutritional state due to severe appetite loss during the administration of quetiapine. A switch to risperidone resulted in the increase of HOMA-β and appetite promotion in the present case.

Hypoglycemia Induced by Second-Generation Antipsychotics

Suzuki et al[5] reported 3 cases of hypoglycemia induced by SGAs (quetiapine, risperidone, and olanzapine) in nondiabetic patients with schizophrenia. Researchers[6] also reported a case of hypoglycemia induced by quetiapine in a patient with schizophrenia that improved after a switch to blonanserin, another SGA. Watanabe et al[7] reported a case of hypoglycemia induced by dumping syndrome following surgery for gastric cancer in a patient with schizophrenia treated with olanzapine. Mondal et al[8] reported oral aripiprazole-induced hypoglycemia in a case of psychosis with Parkinson's disease. In their case,[8] dechallenge and rechallenge with aripiprazole confirmed the close relationship between administration of aripiprazole and onset of hypoglycemic events. Haruta et al[9] reported a case of olanzapine-induced hypoglycemia in anorexia nervosa. In their case,[9] hyperinsulinemia was associated with hypoglycemia as seen in our patient. Omi et al[10] reported a case of hypoglycemia associated with hyperinsulinemia induced by paliperidone in a patient with schizophrenia. Nagamine[11] reported 3 cases of hypoglycemia associated with insulin hypersecretion following the addition of olanzapine to conventional antipsychotics in a patient with schizophrenia. Rowe et al[12] reported a case of neonatal hypoglycemia following maternal olanzapine therapy during pregnancy in a patient with bipolar disorder.

Table 1. Changes in Glucose and Insulin With Altered Medication

Measure	Oral Medications	
	Quetiapine 25 mg, Mirtazapine 15 mg[a]	Risperidone 0.5 mg, Mirtazapine 15 mg[b]
Body mass index	10.9	13.8
Fasting blood glucose	69 mg/dL	80 mg/dL
Fasting blood insulin	0.9 μU/mL	10.1 μU/mL
2-hour blood glucose with OGTT	152 mg/dL	62 mg/dL
2-hour blood insulin with OGTT	234.3 μU/mL	10.6 μU/mL
HOMA-IR score	0.15	2
HOMA-β score, %	5.4	214

[a]9 days after quetiapine initiation.
[b]1 month after quetiapine discontinuation.
Abbreviations: OGTT = oral glucose tolerance test (taken 2 hours after a meal), HOMA = Homeostatic Model Assessment, HOMA-β = insulin secretion ability, HOMA-IR = insulin resistance index.

Although van Winkel and De Hert[16] demonstrated that there was little evidence that SGAs induce reactive hypoglycemia, the number of reports[5–12] on hypoglycemia induced by SGAs has increased. There are several hypotheses on how SGAs induce hypoglycemia.[10] The secretion of insulin by pancreatic β cells might be enhanced by atypical antipsychotics and consequently cause hypoglycemia, while SGAs seem to differ in their effect on insulin release in vitro.[17,18] SGAs might antagonize muscarinic receptors so that insulin secretion continues after glucose levels return to normal, leading to hypoglycemia. Some studies[19] also reported that SGAs significantly reduce glucose levels through induction of insulin release, and the effects might be caused by its potent antagonistic activity against α_2-adrenoceptors. Patients with severe emaciation, as seen in the present case, can easily develop hypoglycemia because of deficient stored glucose levels.[9,11]

CONCLUSION

Complaints of hypoglycemia resemble the sedative effect of antipsychotics. As such, clinicians may overlook hypoglycemia in patients with psychiatric disorders. The present case suggests that, as clinicians, we should bear in mind the potential for hypoglycemia induced by antipsychotics.

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