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Hypoglycemia with atypical antipsychotics, but not with typical antipsychotics: A case report

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ABSTRACT

Atypical antipsychotics cause hypoglycemia as a rare metabolic adverse effect in patients without diabetes. However, its mechanism is not sufficiently clarified. In the present case, a patient with schizophrenia presented with hypoglycemia induced by risperidone and olanzapine after becoming generally debilitated, but not by haloperidol. A complex interaction of serotonergic and adrenergic pathways with atypical antipsychotics may play a role in hypoglycemia. When prescribing atypical antipsychotics for patients, clinicians should be careful not only about the amount and character of the antipsychotics, but also the general status of the patients.

Keywords: atypical antipsychotics, schizophrenia, hypoglycemia, insulin secretion, haloperidol

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Introduction

Atypical antipsychotics are as effective for positive symptoms in patients with schizophrenia with less extrapyramidal symptoms than typical antipsychotics [1]. Recently, they have been widely used in the treatment of various psychiatric disorders for not only schizophrenia, but also bipolar disorder and others [2]. However, atypical antipsychotics have metabolic adverse effects, such as insulin resistance and glucose intolerance [3], which may increase the risk of developing diabetes, result in cardiovascular events, and finally increase the mortality risk [4]. Hypoglycemia is one of the rare adverse effects associated with atypical antipsychotics. A previous study suggested that elderly diabetic patients on antipsychotic medication had a higher risk of hypoglycemia than those not on antipsychotic medication [4]. Furthermore, several reports suggested that psychiatric patients could develop hypoglycemia induced by atypical antipsychotic medications without diabetes [5-7]. However, its mechanism has not been sufficiently clarified. In this report, the case of a patient with schizophrenia taking risperidone over many years who suddenly presented with hypoglycemia after becoming generally debilitated is presented. His hypoglycemia induced by antipsychotics recovered not with atypical antipsychotics, but with haloperidol treatment. Informed consent was obtained from the patient to publish this case report.

Case Presentation

This is the case of a 60-year-old man with schizophrenia. When he was 30 years old, he presented with gradual onset of negative symptoms such as abulia and autosynnoia. When he was 34 years old, he presented with persecutory delusions and was

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violent with family members. He was then admitted to a psychiatric hospital and diagnosed with schizophrenia. He took antipsychotic medications and was discharged after 3-month inpatient care. He was treated as an outpatient with typical antipsychotics for more than 10 years. When he was 48 years old, he was admitted to the hospital because of a relapse. He was treated with risperidone 6 mg/day and discharged after 3 months on risperidone. However, at 58 years of age, he arbitrarily stopped the risperidone because of general fatigue. His symptoms then gradually worsened. Eight months later, he was admitted to hospital and was given risperidone 3 mg/day. At admission, blood examination showed that his hemoglobin (Hb) was markedly decreased to 2.8 (normal range 13.5-17.6) g/dl. He was transferred to a general hospital and treated for a hemorrhagic gastric ulcer for about 1 month. However, 3 months later, his hemorrhagic gastric ulcer relapsed, and he was confined to his bed. Therefore, he was re-admitted to the general hospital. While in the hospital, he was fasted and risperidone was stopped. He was treated for hemorrhagic gastric ulcer and started on rehabilitation for disuse muscle atrophy. However, his psychiatric symptoms worsened. Therefore, he took risperidone starting at 0.5 mg/day, gradually increasing the dose to 6 mg/day. Two weeks after taking risperidone 6 mg/day, he suddenly presented with disturbance of consciousness. Echocardiography and, head and abdominal computed tomography (CT) did not show any organic illness responsible for his consciousness loss. Blood examination showed that his blood sugar (BS) was 50 (normal range 70-110) mg/dl, and hypoglycemic coma was diagnosed. His oral glucose tolerance test (OGTT) with 10% dextrose solution showed that immunoreactive insulin (IRI) was increased, and the decreased BS was poorly responsive. The Homeostatic Model Assessment-insulin resistance (HOMA-IR) was 0.21 (insulin resistance index; normal range <2.5), the Homeostatic Model Assessment-insulin resistance-β (HOMA-β) was 10.1% (index of insulin secretion ability; normal range 30-100%), the Insulinogenic Index was 0.39 (index of insulin secretion ability; normal range >0.4), and the Matsuda Index was 17.99 (insulin sensitivity index; normal range >3.0). Abdominal CT did not show any organic illness responsible for his hypoglycemia, such as pancreatic cancer. These data suggested that increased insulin resistance and abnormal insulin secretion had occurred without any organic illness. Therefore, risperidone-induced hypoglycemia was suspected, and risperidone was quickly stopped. His hypoglycemic coma then improved. On the repeat OGTT, the data were improved: HOMA-IR 0.14, HOMA-β 324.0%, Insulinogenic Index 0.44, and Matsuda Index 51.62. However, his psychiatric symptoms worsened without antipsychotic treatment. Therefore, his medication was changed to olanzapine, but his hypoglycemia continued from the following day, and he again presented with hypoglycemic coma. The result of the OGTT was the same as with risperidone: HOMA-IR 0.09, HOMA-β -42.0%, Insulinogenic Index 1.26, and Matsuda Index 28.38. Thus, he was transferred to our hospital to optimize his medication. On admission to our hospital, his body mass index (BMI) was 14.8 kg/m^2, and malnutrition was suspected. Blood examination showed Hb 8.8 g/dl, BS 76 mg/dl, HbA1c 4.4% (normal range 4.6-6.2%), cortisol 16.4 (normal range 4.3-22.4) μg/dl, human growth hormone 1.93 (normal range 0.05-3.60) ng/ml, IRI 3.9 (normal range 2.19-9.89) uU/ml, and adrenocorticotropic hormone 62.6 (normal range 7.2-63.3) pg/ml. Therefore, there was no evidence of any organic illnesses responsible for hypoglycemia, such as insulinoma, Addison's disease, or growth hormone deficiency, and atypical antipsychotic-induced hypoglycemia was diagnosed. Therefore, the antipsychotics were switched to haloperidol 4.5 mg/day. His BS then stabilized around 100 mg/dl. Since taking haloperidol, hypoglycemia has not been observed, and his psychiatric symptoms improved. The OGTT was repeated and showed that IRI was excessively increased, but the decrease of BS was responsive. HOMA-IR was 0.53, HOMA-β was 159.4%, the Insulinogenic Index was 2.54, and the Matsuda Index was 11.84. All OGTT results are shown in Table 1. Thus, he was transferred to the psychiatric hospital to receive psychiatric rehabilitation. The dose of haloperidol was subsequently increased to 18 mg/day and has been continued for more than two years, with no further evidence of hypoglycemia.

Discussion

A case of postprandial hypoglycemia with increased insulin resistance and secretion induced by two atypical antipsychotics, risperidone and olanzapine, but not by haloperidol, was reported. As shown in Table 1, insulin resistance on the OGTT was increased by the atypical antipsychotics.

With respect to the affinities of receptor profiles be-

Table 1. Changes in blood sugar and immunoreactive insulin before and after an oral glucose tolerance test with no antipsychotic medication, risperidone, olanzapine, and haloperidol

OGTT	Before		After 30 mins		After 60 mins		After 120 mins		After 180 mins	
	BS (mg/dl)	IRI (μIU/ml)	BS	IRI	BS	IRI	BS	IRI	BS	IRI
No antipsychotic medication	64	0.9	79	7.6	133	7.2	109	6	102	7.9
Risperidone 3 mg/day	95	0.9	162	27.6	182	38.9	126	8.6	137	16.1
Olanzapine 10 mg/day	57	0.7	122	82.7	95	37.1	54	4.7	57	2.2
Haloperidol 4.5 mg/day	70	3.1	89	51.4	78	47	82	39.3	59	6.7

BS, blood sugar; IRI, immunoreactive insulin; OGTT, oral glucose tolerance test

tween these antipsychotics, risperidone and olanzapine have higher binding affinities for serotonin receptors than haloperidol [2]. Recently, some studies reported that there is a positive association between serotonin and insulin secretion with gestational diabetes [8, 9]. In addition, olanzapine or quetiapine might be associated with an increased risk of gestational diabetes [10]. It has been reported that blockade of $5HT_{2B}$ receptors causes pancreatic β cell expansion and glucose intolerance in pregnant mice [8]. According to the affinities for 5 HT_{2B}, risperidone and olanzapine have higher binding affinities for serotonin receptors than haloperidol [11]. However, a previous report showed that switching to blonanserin, one of the atypical antipsychotics, improved quetiapine-induced hypoglycemia [7]. It appears that the hypoglycemia induced by atypical antipsychotics cannot be sufficiently explained by the serotonergic system alone. Previous reports suggested that adrenaline receptor (α_2) antagonists increased insulin secretion and reduced blood glucose levels [12, 13]. Risperidone has a much higher affinity for α_2 than haloperidol, and olanzapine's affinity is also higher than that of haloperidol [2]. In the present case, these complex serotonergic and adrenergic pathways may have played a role in the hypoglycemia induced by the atypical antipsychotics.

On the other hand, this patient took risperidone for many years, but he did not present with hypoglycemia until his general status deteriorated. In fact, his doses of risperidone were lower when he presented with hypoglycemia than they had been earlier. It has been reported that, in patients with or without diabetes who were admitted to internal medicine units, there was an association between increased malnutrition risk and hypoglycemia [14].

With respect to the association between general debility and hypoglycemia induced by antipsychotics, it was reported that a patient presented with severe hypoglycemia induced by haloperidol following a hematopoietic stem cell transplant [15]. Previous studies suggested that autophagy might be activated by general debility, such as malnutrition and muscle atrophy, and autophagy in pancreatic β cells might be associated with insulin secretion [16, 17]. In the present case, the patient's general debility, such as the severe anemia and disuse muscle atrophy, may have activated autophagy and caused abnormal insulin secretion and resistance. Such complex factors may have then caused the hypoglycemia induced by risperidone and olanzapine in the present case. Therefore, if the patient had originally taken haloperidol, these factors, that haloperidol has lower affinities for serotonergic and adrenergic receptors than risperidone and olanzapine, and that the general status of this patient was gradually improved, could have prevented the development of severe hypoglycemia. When clinicians prescribe atypical antipsychotics for patients, they should always be aware of the possibility for not only increased, but also decreased blood glucose levels, and they should take into account the general status of the patients. When clinicians prescribe atypical antipsychotics for patients, they should always be aware of the possibility for not only increased, but also decreased blood glucose levels, and they should be careful for general status of patients.

Authors' contributions

SO wrote original-draft. MA was a doctor in charge of the case and gathered the information. HS and JI reviewed the manuscript. SU supervised the manuscript

Ethical Consideration and Consent for publication

Informed consent was obtained from the patient to

publish this case report.

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