Severe Hyperglycemia Induced by Olanzapine was Improved with a Recovery of Insulin Secretion after Switching to Risperidone and Introducing Insulin Therapy

Masaru Nakamura¹ and Takahiko Nagamine²

Abstract

A 35-year-old woman, diagnosed as schizophrenia and treated with olanzapine for nearly 30 months, consulted our department because of severe hyperglycemia. The use of antipsychotics, switching from olanzapine to risperidone, and a one-month introduction of insulin therapy resulted in the decrease of pre-prandial blood glucose levels and the increase of insulin levels (269 to 128 mg/dL, 5.6 to 21.8 μU/mL). A higher level of insulin resistance as measured by HOMA-IR after the improvement of hyperglycemia (3.6 vs. 6.8) suggested that the long use of olanzapine reduced insulin secretion. Based on this case, impairment of pancreatic β-cells caused by olanzapine might be reversible.

Key words: olanzapine, insulin secretion, schizophrenia, HOMA-IR

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Introduction

Olanzapine is known to cause hyperglycemia and other metabolic effects. The mechanism of these abnormalities still remains unclear and it is difficult to comprehend. We present a case of hyperglycemia, which suggests that olanzapine affects insulin secretion and its effect is reversible.

Case Report

A 35-year-old Japanese female patient who had been treated for schizophrenia with olanzapine (15 mg daily) for about 30 months was referred by a psychiatrist to consult our department of internal medicine because of post-prandial hyperglycemia. She had no family history of type 2 diabetes mellitus. Seven months before consultation, her annual serum glucose level of 2 hours after meal and HbA1c examination had been normal (116 mg/dL, 5.6%), and recently, at one month before consultation, the levels were increased (459 mg/dL, 12.6%). Olanzapine was withdrawn because of diabetes mellitus and risperidone (3 mg daily) was introduced for one month, with no improvement of high glucose level (481 mg/dL). During the previous 6 months, she had lost 6 kg (body mass index: 26.5 kg/m²) and complained of thirst. Laboratory examination on admission revealed a high level of fasting glucose (269 mg/dL) with a high level of fasting triglyceride. The GAD (glutamic acid decarboxylase) antibody and IA-2 (antiinsulinoma-associated protein-2) antibody were negative.

While continuing treatment for schizophrenia with risperidone, we started ultra short-acting insulin therapy, adjusted according to every pre-prandial blood glucose level. The clinical course is shown in Fig. 1. After the introduction of insulin therapy, glycemic control was dramatically improved, although there had been no remarkable change in her life style, diet or exercise. Gradual reduction in insulin requirement, from 22 U/day to 4 U/day, was observed in one month. We examined fasting serum insulin and C-peptide level and urine C-peptide area, as shown in Table 1. The endogenous insulin secretion increased with the improvement of hyperglycemia. The decrease of average pre-prandial blood glucose level resulted in the discontinuation of insulin therapy and switching to oral therapy of α-glycosidase in-

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Figure 1. Clinical course of the changes in fasting blood glucose and insulin dose are shown. A gradual reduction in insulin requirement and preprandial blood glucose were observed. In this figure, the data presented are from every other day.

Table 1. Insulin Secretory Function

<table>
<thead>
<tr>
<th>Time point</th>
<th>26 Dec</th>
<th>13 Jan</th>
<th>9 Feb</th>
<th>17 Feb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>269</td>
<td>128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting serum insulin (µU/mL)</td>
<td>5.6</td>
<td>21.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>3.6</td>
<td>6.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting serum C-peptide (µU/mL)</td>
<td>2.9</td>
<td>3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overnight urine C-peptide (µg/day)</td>
<td>150</td>
<td>271</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The data were obtained during the hospital course. The endogenous insulin secretion recovered after the insulin therapy.

Discussion

The changes of atypical antipsychotics in the present case can be summarized as follows: 1) after an improvement of hyperglycemia, the HOMA-IR (Homeostasis model assessment) value was 6.8, as having severe insulin resistance, 2) before the introduction of insulin therapy, HOMA-IR value was 3.6, as having mild insulin resistance with reduction of insulin secretion, 3) improvement of hyperglycemia was shown after a discontinuation of olanzapine, which suggested a direct effect on insulin secretion, and 4) an insulin resistance may have existed, the long use of olanzapine induced a reduction of insulin secretion, and severe hyperglycemia occurred.

Evidence for direct metabolic effects of olanzapine has been provided by a study (1), in which insulin resistance was measured by HOMA-IR after oral glucose tolerance test adjusting for BMI and eliminating weight increase as a factor. They showed that in comparison to risperidone and other conventional antipsychotics, clozapine and olanzapine caused insulin resistance (1). In a study in non-obese, non-diabetic subjects, Henderson et al (2) found that HOMR-IR and leptin levels were elevated following treatment with clozapine and olanzapine, again indicating insulin resistance. Nagamine (3) also reported hypoglycemia associated with insulin hypersecretion following the addition of olanzapine to conventional antipsychotics in 3 cases. They considered that before causing obesity, olanzapine induced insulin resistance. From the above studies olanzapine would be expected...
to promote insulin secretion. In an in vitro experiment, Melkersson (4) exposed pancreatic β-cells to clozapine and olanzapine and found that both agents directly induced insulin secretion.

However, in the present case, a reduction of insulin secretion, not insulin resistance was associated with hyperglycemia. The M3 muscarinic receptor is the major muscarinic receptor that is present on the pancreatic β-cell. These receptors play a key role in maintaining proper insulin release and glucose homeostasis in vitro (5). Impaired glucose tolerance and reduction in insulin secretion was found in mice lacking the M3 muscarinic receptor in pancreatic β-cells and it has been suggested that antagonism of β-cell M3 receptor may increase the risk of hyperglycemia and diabetes in humans (5). Johnson et al (6) found that in vitro low concentration of olanzapine and clozapine inhibited cholinergic-induced insulin secretion by blocking muscarinic M3 receptor activity. Numerous authors have suggested that a high M3 binding affinity could have a diabetogenic effect. In fact, M3 affinity is even considered to be the best predictor of antipsychotic-induced diabetes (7). Olanzapine has the highest binding affinity with the M3 receptor among other atypical antipsychotics (8), and it has very broad receptor-binding profiles such as Histaminergic H1, Serotonergic 5-HT2C, Adrenergic α2 and M3. Probably it is not just one of these pathways that is responsible for the effect on insulin-glucose homeostasis (9); it is more likely these and possible other pathways as well, overlap and enhance each other.

In the present case, the patient was fortunately relieved from insulin therapy and the severe hyperglycemia induced by a long use of olanzapine. To our knowledge, this is the first report suggesting that the reduction of insulin secretion caused by olanzapine is reversible if the diagnose and therapy for hyperglycemia are sufficiently early. In conclusion, when prescribing atypical antipsychotics including olanzapine, clinicians should consider close monitoring of the parameters such as serum glucose including insulin level.

References


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