Hypoglycemia associated with insulin hypersecretion following the addition of olanzapine to conventional antipsychotics

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Abstract: After a violent episode, a 47-year-old Japanese man with chronic treatment-resistant schizophrenia was admitted to our hospital and treated with conventional antipsychotics. After 3 years, olanzapine was added. Four days later, he lost consciousness and blood tests revealed marked hypoglycemia, increased insulin levels, and a homeostasis model assessment of insulin resistance of 2.5. He recovered rapidly after intravenous injection of glucose. He had no history of loss of consciousness, was not obese and did not have any risk factors for hypoglycemia. Similar episodes occurred in the early morning of the fifth and sixth days following the olanzapine administration. Each time there was the same response to intravenous glucose. Olanzapine was discontinued on the seventh day and, after one year, replaced by risperidone. Since then (2 years ago), his schizophrenic symptoms have been in partial remission and he has had no further hypoglycemic episodes. In view of the possible induction of hypoglycemia with olanzapine, even in the absence of any risk factors, and in the absence of any major differences in efficacy, it is a reasonable strategy to select an agent such as risperidone which has more favorable side-effect profile.

Keywords: metabolic syndrome, hypoglycemia, insulin resistance, schizophrenia, second-generation antipsychotics

Olanzapine is known to cause hyperglycemia and hyperlipidaemia. The mechanism of these metabolic abnormalities is still unclear. We present a case of hypoglycemia which suggests that olanzapine affects insulin secretion.

A Japanese man (aged 47) with chronic schizophrenia had delusions and hallucinations that were refractory to treatment and was repeatedly admitted to psychiatric hospitals. He had become violent toward his family and was admitted to Seiwakai-Kitsunan Hospital as a long-term in-patient and treated with haloperidol 12 mg/day, levomepromazine 150 mg/day, flunitrazepam 2 mg/day, and biperiden 3 mg/day, without side-effects for 3 years.

In view of the lack of improvement in the patient’s psychiatric condition, it was decided to add an atypical antipsychotic agent to the treatment regimen and olanzapine was introduced (10 mg nocte) after blood tests showed no metabolic abnormalities (case 1, Table 1). Four days later, he suddenly lost consciousness in the morning, while walking in the ward, but did not appear to have a seizure. A blood sample was taken while he was unconscious and revealed severe hypoglycemia and elevated insulin levels while triglycerides were normal (Table 1). A bolus injection of 20 mL 50% glucose was administered intravenously and he rapidly regained consciousness. Similar episodes occurred in the early morning of the fifth and sixth days following the onset of treatment with olanzapine. Each time there was the same response to intravenous glucose. The patient did not have a history of loss of consciousness or seizures, his body mass index (BMI) was 19.8, and he did not have any conditions associated with hypoglycemia, such as gastrectomy or hepatic dysfunction. Electroencephalography revealed no abnormalities.
Olanzapine was withdrawn on the seventh day and there were no further episodes of hypoglycemia or loss of consciousness (Table 1). Treatment with the conventional antipsychotics continued for approximately 1 year, at which time risperidone, an atypical antipsychotic agent, was introduced (2 mL oral solution (1 mg/mL nocte) to the regimen and for the past 2 years his chronic schizophrenia has been in partial remission on 3 mL daily. There have been no hypoglycemic episodes for 3 years and fasting blood tests do not show any abnormalities (Table 1). Biochemical data from two other patients (cases 2 and 3) who developed asymptomatic hypoglycemia while taking olanzapine at this hospital are also shown in Table 1.

Olanzapine is known to cause hyperglycemia and elevated triglyceride levels. In a recently published randomized controlled trial with discontinuation of antipsychotic agents as an indicator of intolerance, discontinuation because of weight increase and metabolic abnormalities was significantly more common for olanzapine (Lieberman et al 2005) than for other antipsychotics. Osser et al (1999) suggested that the metabolic abnormalities caused by olanzapine are usually related to weight gain and the associated insulin resistance.

In the present case, however, olanzapine resulted in hypoglycemia, not hyperglycemia, and it may be that there is a common metabolic abnormality; namely, olanzapine-induced insulin resistance. In the present case, insulin levels were elevated during the episodes of hypoglycemia following each dose of olanzapine, which suggests the possibility of delayed insulin hypersecretion.

Evidence for direct metabolic effects of olanzapine has been provided by a study (Newcomer et al 2002) in which insulin resistance was measured by homeostasis model assessment (HOMA).

| Table 1 Metabolic markers prior to, during, and after olanzapine treatment |
|---------------------------------------------------------------|
| **Case 1** | **Case 2** | **Case 3** |
| **Gender** | Male | Male | Male |
| **Age (years)** | 52 | 58 | 44 |
| **BMI** | 19.8 | 18.8 | 19.6 |
| **Height (cm)** | 154 | 158 | 153 |
| **Weight (kg)** | 47 | 47 | 46 |
| **Medication prior to olanzapine** | HAL 12 mg; LP 150 mg; | RIS 4 mg | RIS 4 mg |
| **Olanzapine dose** | 10 mg | 5 mg | 15 mg |
| **Loss of consciousness** | Yes | No | No |
| **Fasting plasma glucose (mg/dL)** | 86 | 85 | 84 |
| **Before olanzapine** | 44 | 57 | 64 |
| **On olanzapine** | 87 | – | – |
| **After olanzapine withdrawal and the addition (1 year later) of risperidone 3 mg** | – | – | – |
| **Fasting serum insulin (µU/mL)** | 5 | 5 | 4 |
| **Before olanzapine** | 23 | 17 | 40 |
| **On olanzapine** | 6 | – | – |
| **After olanzapine withdrawal and the addition (1 year later) of risperidone 3 mg** | – | – | – |
| **Insulin resistance (HOMA)** | 1.06 | 1.05 | 0.83 |
| **Before olanzapine** | 2.50 | 2.39 | 6.32 |
| **On olanzapine** | 1.29 | – | – |
| **After olanzapine withdrawal and the addition (1 year later) of risperidone 3 mg** | – | – | – |
| **Fasting plasma triglyceride (mg/dL)** | 92 | 69 | 90 |
| **Before olanzapine** | 88 | 64 | 83 |
| **On olanzapine** | 96 | – | – |
| **After olanzapine withdrawal and the addition (1 year later) of risperidone 3 mg** | – | – | – |

*case described in this paper

**Abbreviations:** BMI, body mass index; HAL, haloperidol; HOMA, homeostasis model assessment; LP, levomepromazine; RIS, risperidone.
assessment (HOMA-IR) after oral glucose tolerance testing, adjusting for BMI and eliminating weight increase as a factor. They showed that in comparison to risperidone and conventional antipsychotics, clozapine and olanzapine caused insulin resistance (Newcomer et al 2002). In a study in non-obese, non-diabetic subjects, Henderson et al (2005) found that HOMA-IR and leptin levels were elevated following treatment with clozapine and olanzapine, again indicating insulin resistance. Using frequently sampled intravenous glucose tolerance test (FSIVGTT) and calculating insulin sensitivity indices using minimal model analysis they found that insulin sensitivity was significantly lower with clozapine and olanzapine treatment than with risperidone. They considered that before causing obesity, olanzapine induces insulin resistance.

Thus from the above studies olanzapine would be expected to promote insulin secretion. In the case presented here the patient experienced episodes of hypoglycemia, not hyperglycemia, and each time his insulin levels were high, and as a result the HOMA-IR was high. In an in vitro experiment, Melkersson (2004) exposed pancreatic beta-cells to clozapine and olanzapine and found that both agents directly induced insulin secretion. To our knowledge, we report here the first case of hypoglycemia associated with insulin hypersecretion.

Usually, even if olanzapine stimulates insulin secretion, homeostatic mechanisms act to regulate blood sugar levels and prevent the onset of hypoglycemia. The present patient is slim, with low fasting blood glucose and triglyceride levels, so he may lack reserve capacity with regard to glucose homeostasis, which may be the reason why he developed hypoglycemia early in the morning before breakfast. Although the clinical presentation was a series of hypoglycemic episodes, the HOMA-IR was higher than at other times, indicating the underlying problem was insulin resistance. The patient was successfully switched to risperidone oral solution 1 year later, without recurrence of hypoglycemia, suggesting that the hypoglycemic episodes were a direct metabolic effect of olanzapine.

Although biochemical data are not available after olanzapine discontinuation, two other patients at this hospital have experienced asymptomatic hypoglycemic episodes associated with olanzapine (Table 1). All three cases of hypoglycemia were males of slim build, with low blood glucose and triglyceride levels prior to starting on olanzapine. Although it may initially appear paradoxical, the possibility of metabolic abnormalities, particularly hypoglycemia, should be considered in the early stages of introducing olanzapine to the treatment regimen of slim, male patients. Indeed, it could be argued that a systematic search for indicators of insulin resistance should be carried out in all slim male patients within a few days of starting olanzapine after having established baseline values before treatment.

References
Henderson DC, Cagliero E, Copeland PM, et al. 2005. Glucose metabolism in patients with schizophrenia treated with atypical antipsychotic agents. Arch Gen Psychiatry, 62:19–28.
Lieberman JA, Stroup TS, McEvoy JP, et al. 2005. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med, 353:1209–23.
Merkersson K. 2004. Clozapine and olanzapine, but not conventional antipsychotics, increase insulin release in vitro. Eur Neuropsychopharmacol, 14:115–9.
Newcomer JW, Haupt DW, Fucetola R, et al. 2002. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. Arch Gen Psychiatry, 59:337–45.
Osser DN, Najarian DM, Dufresne RL. 1999. Olanzapine increases weight and serum triglyceride levels. J Clin Psychiatry, 60:767–70.
