

Direct metabolic effects of risperidone and olanzapine in Japanese schizophrenic patients

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In clinical practice, the high incidence of metabolic abnormalities, such as diabetes and hyperlipidemia, seen in schizophrenic patients are the result of a complex interaction of a number of factors, including lifestyle, overactivity of the hypothalamic-pituitary-adrenal axis, and antipsychotic medication. Antipsychotic-induced metabolic abnormalities have been thought to be due to insulin resistance caused by obesity, which is a major side-effect of antipsychotics. However, there is increasing evidence that second-generation antipsychotics can also have direct metabolic effects.

We investigated two similar groups of 9 non-obese, non-diabetic Japanese schizophrenic patients taking either risperidone or olanzapine as monotherapy for 3–6 weeks with no changes in their treatment for at least 3 weeks. The published Japanese definitions for obesity (BMI >25, waist measurement at umbilicus level >85 cm for males, >90 cm for females) and diabetes (fasting glucose > 110 mg/dL) were used (Matsuzawa et al 2005).

Metabolic markers (glucose, insulin, triglycerides, total cholesterol, and high-density lipoprotein cholesterol) were measured in blood samples taken after 12 h fasting. Subjects then ingested a 110 g glucose tolerance test cookie (Harano et al 2006) and blood was taken 2 h later for measurement of glucose, insulin, triglycerides, and remnant-like lipoprotein particles (RLP) cholesterol levels. Insulin resistance was assessed by the homeostasis model assessment of insulin resistance (HOMA-IR) (Emoto et al 1999). RLP were measured as the unbound serum fraction in an immuno-affinity mixed gel using monoclonal antibodies to apoA-I and apoB100 (Nakajima et al 1996). RLP-cholesterol levels were determined as the cholesterol fraction.

Fasting values and those obtained 2 h after the glucose tolerance test are shown in Table 1. Plasma glucose levels remained within normal limits for both groups although those in the olanzapine group were significantly increased after the test compared with fasting levels. Insulin levels were significantly increased to a similar extent in both groups after the glucose tolerance test. No insulin resistance was seen in any patient.

The triglyceride levels were significantly increased compared to fasting levels in the olanzapine group but not in the risperidone group. The value over the normal limit (>150 mg/dL) indicates that lipid metabolic abnormalities may occur in the olanzapine group. In addition, the level of RLP-cholesterol in the olanzapine group was also significantly increased compared to the risperidone group.

Higher fasting serum insulin levels have been found in schizophrenic patients treated with clozapine compared with those treated with conventional antipsychotics, suggesting possible insulin resistance (Melkersson et al 1999). Similarly treatment with olanzapine

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Table 1 Carbohydrate and lipid metabolism markers

	Risperidone-treated patients	Olanzapine-treated patients
	n = 9	n = 9
Glucose (mg/dL)– fasting	88.1 ± 8.1	92.6 ± 10.5
• after glucose tolerance cookie	99.6 ± 9.7	109.0 ± 15.0*
Insulin (μU/L)–fasting	5.4 ± 2.6	5.5 ± 3.3
• after glucose tolerance cookie	7.8 ± 1.8**	9.1 ± 2.3*
Triglycerides (mg/dL)–fasting	120.9 ± 27.4	130.4 ± 33.6
• after glucose tolerance cookie	132.6 ± 24.2	171.2 ± 41.7*
Total cholesterol (mg/dL)–fasting	165.2 ± 42.4	171.2 ± 34.5
HDL cholesterol (mg/dL)–fasting	48.8 ± 12.7	48.2 ± 13.1
RLP-cholesterol (mg/dL)	4.3 ± 1.6	7.5 ± 1.0 †
Insulin resistance (HOMA-IR)– fasting	1.19 ± 0.6	1.23 ± 0.7

All values are mean ± SD.

*p < 0.05 **p < 0.01 compared with fasting values.

†p < 0.05 compared with risperidone.

resulted in elevated serum insulin levels compared to baseline values in a 5-month study (Melkersson et al 2000).

These studies suggest that certain antipsychotics can induce insulin resistance. It is not clear, however, from these studies whether the effect results from metabolic syndromes, such as weight gain and obesity, or a direct effect.

Evidence for a direct effect is accumulating. A recent study of non-obese, non-diabetic schizophrenics showed elevated fasting insulin levels with clozapine and olanzapine (Henderson et al 2005). In this study, insulin resistance was significantly reduced in patients on clozapine or olanzapine compared with those on risperidone. In addition, in vitro studies have shown a direct effect of clozapine and olanzapine but not conventional antipsychotics on the stimulation of insulin secretion from pancreatic β-cells (Melkersson 2004).

In the present study, non-obese and non-diabetic patients were selected, so that any lipid metabolic abnormalities that were seen were not due to any metabolic syndrome. Although no insulin resistance was found in the olanzapine treatment group, high levels of triglyceride and RLP-cholesterol were induced by the glucose tolerance cookie test. This suggests that olanzapine has a direct action on lipid metabolism even after relatively short treatment duration (3–24 weeks).

In contrast to the study by Henderson et al (2005), the present study in non-obese, non-diabetic subjects found no difference between patients treated with olanzapine and risperidone in fasting insulin levels which were all within the normal range. A possible reason for this difference between the studies may be the duration of drug treatment. In the Henderson study, the mean duration of treatment with olanzapine was 29.5 months, whereas it was only 12.3 weeks

in the present study. Another possibility is the influence of racial differences. Asian people have reduced insulin secretion compared with Caucasians (Sasahara et al 2004), making it theoretically more difficult to detect metabolic abnormalities from fasting blood samples. This could explain why insulin resistance was not detected in our group of Japanese patients. The glucose tolerance test is clearly useful for earlier detection of lipid metabolic abnormalities. This is especially true for Japanese patients who have reduced insulin secretion compared with Caucasians and their metabolic abnormalities are not easily detected by conventional markers.

Higher levels of RLP-cholesterol have recently been suggested to be a risk factor for arteriosclerosis (Takeichi et al 1999). In a 3-year follow-up study of patients with coronary artery disease, patients with higher RLP-cholesterol (>5.1 mg/dL) had a significantly greater risk of developing coronary events than lower RLP-cholesterol patients (<3.3 mg/dL) (Kugiyama et al 1999). The present study suggests that patients treated with olanzapine should be routinely tested using the glucose tolerance cookie test to determine RLP-cholesterol level as a risk marker for the development of coronary events.

References

- Emoto M, Nishizawa Y, Maekawa K, et al. 1999. Homeostasis model assessment as a clinical index of insulin resistance in type 2 diabetic patients treated with sulfonylureas. *Diabetes Care*, 22:818–22.
- Harano Y, Miyawaki T, Nabiki J, et al. 2006. Development of cookie test for the simultaneous determination of glucose intolerance, hyperinsulinemia, insulin resistance and postprandial dyslipidemia. *Endocr J*, 53:173–80.
- 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.

- Kugiyama K, Doi H, Takazoe K, et al. 1999. Remnant Lipoprotein levels in fasting serum predict coronary events in patients with coronary artery disease. *Circulation*, 8:2858–60.
- Matsuzawa Y. 2005. Metabolic syndrome—definition and diagnostic criteria in Japan. *J Atheroscler Thromb*, 12:301.
- Melkersson KI, Hunting AL, Brismar KE. 1999. Different influences of classical antipsychotics and clozapine of glucose-insulin homeostasis in patients with schizophrenia or related psychoses. *J Clin Psychiatry*, 60:783–91.
- Melkersson KI, Hunting AL, Brismar KE. 2000. Elevated levels of insulin, leptine, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. *J Clin Psychiatry*, 61:742–9.
- Melkersson K. 2004. Clozapine and olanzapine, but not conventional antipsychotics, increase insulin release in vitro. *Eur Neuropsychopharmacol*, 14:115–19.
- Nakajima K, Okazaki M, Tanaka A, et al. 1996. Separation and determination of remnant-like particles in human serum using monoclonal antibodies to apoB100 and apoA-I. *J Clin Ligand Assay*, 19:177–83.
- Sasahara M, Nishi M, Kawashima H, et al. 2004. Uncoupling protein 2 promoter polymorphism—866G/A affects its expression in beta-cells and modulates clinical profiles of Japanese type 2 diabetic patients. *Diabetes*, 53:482–5.
- Takeichi S, Yukawa N, Nakajima Y, et al. 1999. Association of plasma triglyceride-rich lipoprotein remnants with coronary atherosclerosis in cases of sudden cardiac death. *Atherosclerosis*, 142:309–15.

