Olanzapine Induces Insulin Resistance: Results From a Prospective Study

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Background: The aim of this study was to compare glucose metabolism in patients with schizophrenia receiving olanzapine with that in control subjects.

Method: We conducted a prospective, controlled, open study comparing body weight, fat mass, and indices of insulin resistance/sensitivity in 10 olanzapine-treated patients with ICD-10 schizophrenia (olanzapine dose range, 7.5–20 mg/day) with those of a group of 10 mentally and physically healthy volunteers. Weight, fat mass, and indices of insulin resistance/sensitivity were assessed over individual 8-week observation periods from November 1997 to October 1999.

Results: Fasting serum glucose and fasting serum insulin increased significantly in the olanzapine-treated patients ($p = .008$ for glucose and $p = .006$ for insulin). The homeostasis model assessment (HOMA) index for beta cell function did not change significantly in the olanzapine-treated patients, whereas the HOMA index for insulin resistance did increase ($p = .006$). In the control group, these parameters were stable. A significant increase in body weight ($p = .001$) and body fat ($p = .004$) was seen in patients treated with olanzapine, while the control group showed no significant changes.

Conclusion: This study indicates that the disturbances in glucose homeostasis during antipsychotic treatment with olanzapine are mainly due to insulin resistance. However, beta cell function remains unaltered in olanzapine-treated patients. We conclude that treatment with some second-generation antipsychotic drugs may lead to insulin resistance.

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Since the introduction of second-generation antipsychotic agents, such as clozapine and olanzapine, these drugs have increasingly replaced the use of classical antipsychotics. Their superior activity against negative symptoms of schizophrenia, decreased extrapyramidal symptoms, and better overall tolerability make them drugs of first choice.[1–3]

The use of second-generation antipsychotics is associated with some adverse events that, among other adverse events, affect the metabolic system. Clozapine and olanzapine induce the most significant weight gain,[4–10] which is mainly due to an increase in body fat.[11] Furthermore, clozapine and olanzapine have been linked with the induction of hypertriglyceridemia,[12–16] and both of these antipsychotics have been associated with disturbances in glucose metabolism.[16–20] In a recent population-based nested case-control study, the odds ratio of olanzapine-treated patients to develop diabetes was estimated to be 5.8.[21]

Olanzapine and clozapine have strong affinities to serotonin (5-HT) and histamine (H) receptors (5-HT_{2C}, 5-HT_{2A}, and H_1 receptors). Blockade of the respective receptors has been linked to weight gain.[6]

Excess body weight increases the risk of death from any cause and from cardiovascular disease in adults aged 30 to 74 years. This risk associated with greater body weight is higher among younger subjects.[22] Furthermore, both the prediabetic and diabetic states have been linked to excess morbidity and mortality due to the development of macrovascular and microvascular diseases.[23,24] In addi-

tion, hypertriglyceridemia associated with small, dense low-density lipoprotein particles and low levels of high-density lipoprotein cholesterol is an independent risk factor for the development of premature atherosclerosis.[25–27]

These metabolic adverse effects of newer antipsychotic drugs—in addition to general health risks—have meaningful clinical implications in the long-term management of schizophrenia and may limit the subjective acceptance of these drugs in patients with schizophrenia.[10]

To explore the pathophysiology of the disturbances in glucose homeostasis induced by antipsychotic treatment, we investigated indices of glucose homeostasis and insulin resistance/sensitivity using a prospective design to study patients with schizophrenia treated with olanzapine and control subjects.

METHOD

Patients and Control Subjects

Ten patients fulfilling ICD-10 diagnostic criteria for schizophrenia consecutively admitted to an inpatient unit of the Department of Psychiatry at the University of Innsbruck, Innsbruck, Austria, and assigned to monotherapy with olanzapine (7.5–20 mg/day) were included in this study. Premedication was washed out for at least 3 days before olanzapine administration. The 10 patients included 8 men and 2 women with a mean age of 30.4 years. An age (mean = 32.2 years) and sex matched (8 men and 2 women) healthy control group was recruited from the hospital staff. Mean individual study observation time was 8.1 weeks during the period November 1997 to October 1999. This report extends findings of a previously published study.[11] All patients gave written informed consent to participate in this study, which was performed according to the guidelines of the Ethical Committee of the Medical Faculty of Innsbruck University.

Analysis of Body Composition

Weight and height were measured at baseline, and weight measures were repeated in weekly intervals. Body composition was determined every 4 weeks by impedance analysis using a multifrequency BIA 2000-M impedance analyzer (Data Input, Hofheim, Germany). Fat free mass and fat mass were determined using Nutri 4 software (Data Input, Hofheim, Germany).

Laboratory Measurements

Blood was drawn after an overnight fast from an antecubital vein into ethylenediaminetetraacetic acid (EDTA)-treated tubes (1.6 mg/mL). Plasma was separated from erythrocytes by centrifugation at 3000 rpm for 10 minutes at 4°C (39°F) immediately after collection. Plasma samples were stored frozen at –80°C (–18°F) until assayed.

Plasma glucose concentrations were measured using a standard enzymatic method (Roche Diagnostic Systems, Basel, Switzerland). Plasma insulin concentrations were measured using a microparticle enzyme immunoassay (Abbott, Vienna, Austria).

The homeostasis model assessment (HOMA) indices for beta cell function and for insulin resistance were calculated as described in detail elsewhere.[28–31]

Statistical Analysis

Descriptive data given are mean values. A paired t test was used for within-group comparisons (week 8 vs. baseline). A t test for independent samples was performed for between-group comparisons with respect to changes (in all investigated parameters) between baseline and week 8. Statistical significance was inferred at a 2-tailed p value of less than .05. Statistical analyses were calculated using SPSS release 8.0 for Windows (SPSS, Chicago, Ill.).

RESULTS

Fasting glucose levels increased significantly from 4.8 mmol/L at baseline to 5.5 mmol/L after a mean medication period with olanzapine of 8.1 weeks ($p = .008$). None of the patients developed overt diabetes or impaired fasting glucose according to American Diabetes Association criteria.[32,33] Fasting insulin concentrations increased significantly from 6.09 μU/mL at baseline to 10.64 μU/mL after the study period ($p = .006$) (Table 1).

As a model of the glucose-insulin feedback system in the overnight-fasted state, we calculated the HOMA index for both beta cell function and insulin resistance. The model consists of a number of nonlinear empirical equations describing the function of tissues involved in glucose regulation. It allows the deduction of beta cell function and insulin sensitivity (or resistance) from pairs of fasting glucose and insulin measurements. The HOMA index for beta cell function remained stable throughout the study period (104.86% at baseline vs. 117.67% at the end of the observation period, respectively, n.s.). In contrast, the HOMA index for insulin resistance increased significantly from a mean of 1.31 $mmol \cdot mU^{-1} \cdot L^{-2}$ to 2.59 $mmol \cdot mU^{-1} \cdot L^{-2}$ in the olanzapine-treated patients ($p = .006$), suggesting induction of severe insulin resistance in these patients (Table 1).

Weight increased by 3.3 kg (7.3 lb) in olanzapine-treated patients during the medication period of 8.1 weeks. The range of weight gain was between 1.2 kg (2.7 lb) and 6.5 kg (14.4 lb). Weight gain was mainly due to an increase in fat mass: patients gained a mean of 2.2 kg (4.9 lb) of body fat. Minimum fat gain was 0.5 kg (1.1 lb); maximum fat gain was 5.0 kg (11.1 lb) (Table 1).

DISCUSSION

Diabetes mellitus is more common in patients with schizophrenia than in the general population.[34] However,

Table 1. Weight, Body Fat, Lean Body Mass, BMI, Glucose, Insulin, and HOMA Indices in Olanzapine-Treated Patients and Comparison Subjects

	Patients					Comparison Subjects					Between-Group Analysis of Change Scores	
	Baseline		Week 8		Analysis	Baseline		Week 8		Analysis		
Measure	Mean	SD	Mean	SD	p Value	Mean	SD	Mean	SD	p Value	df	p Value
Weight (kg)	68.8	11.3	72.1	10.5	.001	70.8	10.2	71.4	10.4	.20	18	.005
Body fat (kg)	13.1	4.5	15.3	4.2	.004	11.9	2.5	12.2	3.6	.72	16	.04
Lean body mass (kg)	54.1	7.7	54.8	7.4	.35	58.6	8.8	59.2	8.2	.39	16	.86
Body mass index (kg/m^2)	22.4	3.0	23.5	2.6	.001	22.1	2.7	22.3	2.9	.13	18	.005
Glucose (mmol/L)	4.8	0.4	5.4	0.5	.008	5.4	0.3	5.4	0.5	.93	17	.009
Insulin (μU/mL)	6.1	2.4	10.6	5.3	.006	8.6	3.6	7.4	4.3	.44	17	.008
HOMA β cell function (%)	104.9	52.7	117.7	48.3	.57	94.4	46.9	78.9	39.3	.24	17	.26
HOMA Insulin resistance ($mmol \cdot mU^{-1} \cdot L^{-2}$)	1.3	0.5	2.6	1.4	.006	2.0	0.8	1.8	1.1	.53	17	.008

Abbreviations: BMI = body mass index, HOMA = homeostasis model assessment.

there is increasing evidence that treatment with at least some second-generation antipsychotics may be associated with the development of diabetes mellitus. Several cases of diabetes induced by clozapine and olanzapine have been reported in recent years.[17,19,35–39] In general, these patients had no family history of diabetes, were taking a dose of olanzapine ranging from 5 to 30 mg/day, and experienced significant weight gain during the medication period. The range from treatment initiation to the development of diabetes was 8 days to 17 months, and, in some instances, diabetes was reversible after olanzapine was discontinued.[19]

In this prospective study, we observed a significant increase in insulin resistance in a small number of patients as determined from the HOMA index, but no changes in beta cell function were found. The patients' clinical characteristics were similar to those observed in previous studies: patients had a mean age of 30.4 years; most had no family history of diabetes; most were lean at the initiation of therapy, with a mean body mass index (BMI) of 22.4 kg/m^2; and most gained weight during therapy. The weight gain was found to be mainly due to an increase in fat mass.[11] According to large epidemiologic studies, weight gain of 1 BMI unit corresponds to an increase in relative risk to develop diabetes mellitus of 2.9 to 4.3 for women[40] and 1.0 to 1.5 for men.[41] Thus, the increase in fat mass, itself, may be a factor leading to an increase in insulin resistance. An increase in insulin resistance occurred in the majority of our study patients. Some patients developed insulin resistance, while not gaining fat, suggesting that an increase in fat mass is not the only factor contributing to the induction of insulin resistance. Also, the prompt onset of diabetes reported in other studies argues against a primary role of weight gain, although it may contribute to later onset diabetes, which has been observed.[20,35]

Which additional or alternative mechanisms could account for the dysregulation of glucose homeostasis induced by olanzapine? The insulin resistance induced by olanzapine treatment is rapid, occurring within days, suggesting that a potent factor distinct from weight gain directly induces insulin resistance. Likely candidates include free fatty acids, leptin, and tumor necrosis factor αTNF-α.[42]

Theoretically, olanzapine could also be a beta cell toxin. There are no overt chemical similarities between olanzapine and known islet toxins. The ring structures of these compounds are not uniform nor are their side chains. In addition, antipsychotic compounds seem to differ in their potency to induce hyperglycemia, with olanzapine and clozapine the most potent substances. Findings on antiislet-autoantibodies, antiglutamic acid decarboxylase antibodies, and human insulin autoantibodies were negative in 1 case report of a 33-year-old white man who presented with diabetic ketoacidosis after initiation of clozapine therapy, suggesting that no autoimmune diabetes was induced.[43] Furthermore, in vitro insulin release from pancreatic beta cells was not modified by olanzapine.[44] Neither olanzapine nor risperidone modulated the in vivo insulin secretory response to prolonged hyperglycemia in healthy volunteers[45] and, as demonstrated in our study, beta cell function was stable throughout the study period. This evidence taken together makes it unlikely that olanzapine has a direct toxic effect on beta cells.

Antipsychotics are dopamine-2 (D2) receptor antagonists. They are commonly associated with serum prolactin elevations due to D2 receptor antagonism in the hypothalamus. Dopamine agonists, such as bromocriptine, are known to decrease blood glucose. Thus, hypothalamic dopamine antagonism may contribute to the dysregulation of glucose homeostasis of antipsychotics. Risperidone, which is a potent D2 receptor antagonist that increases serum prolactin concentrations, has not been associated with drug-induced diabetes, which argues against a major role of D2 receptor antagonism in the development of impaired glucose homeostasis.[19]

CONCLUSION

This study, using a prospective, open, controlled study design, confirms the induction of glucose and insulin homeostasis dysregulation in olanzapine-treated patients. In addition, an analysis of the HOMA indices indicates not that beta cell function is altered but rather that peripheral insulin resistance is induced during olanzapine treatment.

This study reinforces the necessity of regular monitoring of metabolic parameters in patients treated with olanzapine. Due to the induction of insulin resistance within weeks of the initiation of olanzapine intake, prescribing clinicians should consider close monitoring of the parameters of glucose homeostasis early in treatment.

Drug names: bromocriptine (Parlodel and others), clozapine (Clozaril and others), olanzapine (Zyprexa), risperidone (Risperdal).

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