

Effect of Antipsychotic Therapy on Insulin Sensitivity: A Comparison of Olanzapine, Risperidone, and Placebo in Normal Subjects

1. Introduction

Olanzapine (LY170053) is a dopamine, serotonin, cholinergic, histamine, adrenergic receptor antagonist (Moore et al. 1992, 1993) that has been shown to be an effective antipsychotic agent with an "atypical" profile. It is now marketed in an oral dosage form as Zyprexa™ in the United States and other countries. Olanzapine has a well-established safety record. More than 3,000 subjects participated in olanzapine registration trials and in excess of 4 million subjects have been treated with Zyprexa™ in clinical settings. *Although the safety of olanzapine has been well established, literature case reports have described an association of olanzapine treatment and the onset of hyperglycemia. To better understand this association, the literature on the prevalence of diabetes and on the association between diabetes and schizophrenia and antipsychotic use was carefully reviewed, the spontaneous adverse event database for olanzapine was analyzed, one clinical study was initiated, and preparation of additional studies, including the present study, was begun.*

The prevalence of diabetes in the general population rose 33% in the period between 1990 and 1998. This increase was highly correlated with the incidence of obesity, and was observed across all ages, ethnic groups, and education levels (Mokdad et al. 2000). Several studies have implicated schizophrenia as a potential risk factor for developing type 2 diabetes mellitus (DM) (Mukherjee 1999; Dixon et al. 1998; Mukherjee et al. 1996; McKee et al. 1986; Keskiner et al. 1973). These studies report the prevalence of type 2 DM in subjects with schizophrenia to be approximately 2 to 4 times greater than in the general population. On the basis of current data, this amounts to a prevalence of some 14% to 28% among U.S. subjects with schizophrenia. There is some disagreement on this issue, however, as Dvirskii et al. (1997) argues that type 2 DM in schizophrenia is observed less frequently than would be expected based on the prevalence in the general population. Interestingly, Thonnard-Neumann (1968) has found a greater prevalence of type 2 DM among subjects with paranoid type of schizophrenia, even though they had fewer risk factors including less antipsychotic use than subjects with the nonparanoid type. Moreover, the later manifestations and complications of type 2 DM, such as cardiovascular disorders and diabetic retinopathy, were much less frequent among subjects with schizophrenia and type 2 DM than among subjects with type 2 DM alone. These studies suggest that the underlying mechanism of diabetes mellitus associated with schizophrenia may be different than that of type 2 DM.

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The mechanism for the higher prevalence of type 2 DM in schizophrenia is not presently understood. The use of antipsychotic agents has been suggested; however, high incidences of insulin resistance and impaired glucose tolerance (IGT) had been noted in subjects with schizophrenia even before the introduction of antipsychotic agents into clinical practice (Langfeldt 1952; Freeman 1946; Braceland et al 1945; Lorenz 1922).

There is extensive evidence in the literature that both typical and atypical antipsychotic therapy may be associated with impaired glucose metabolism (Erle et al. 1977; Korenyi and Lowenstein 1968; Kamran et al. 1994; Pierides 1997; Popli et al. 1997, Wirshing et al. 1998). One such atypical antipsychotic, risperidone, has a distinct chemical structure but is of the same therapeutic class as olanzapine. Risperidone also appears to alter glucose metabolism. Spontaneous adverse event data for risperidone was obtained from the U.S. Food and Drug Administration under the Freedom of Information Act (FOI). The FDA database was current for reports received through June 1998. Detailed clinical information was not available to assess individual cases. Data indicate that approximately 73 patients per 100,000 experienced some form of impaired glucose metabolism while being treated with risperidone. There has been one case report to date of the development of diabetic ketoacidosis with risperidone (2 mg/day) (Croarkin et al. 2000).

As of 30 April 2000, there were 419 spontaneous adverse event reports clinically indicative of hyperglycemia associated with olanzapine treatment. Of these reports, 120 were accompanied by information that allowed the determination of the time from the first dose of olanzapine to the time of diagnosis of hyperglycemia. Descriptive statistics of days from first dose of olanzapine to the diagnosis of hyperglycemia are shown in Table S013.1.

Table S013.1. Descriptive Statistics of Days from First Dose of Olanzapine to the Diagnosis of Hyperglycemia

Quantiles		Days	Summary Statistics	Days
Maximum	100.0%	1095	Mean	164
	99.5%	1095	Std Dev	209
	97.5%	936	Std Error Mean	19
	90.0%	395	Upper 95% Mean	202
3rd Quartile	75.0%	203	Lower 95% Mean	127
Median	50.0%	90	N	120
1st Quartile	25.0%	30		
	10.0%	13		
	2.5%	3		
	0.5%	0		
Minimum	0.0%	0		

Of the 419 reports, approximately half included enough information to determine that diabetes mellitus was a pre-existing condition in 66% of the evaluable cases. Although

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there were approximately 70 subjects without a known history of diabetes, the majority of these had one or more of the following risk factors for the development of diabetes: 1) family history of diabetes; 2) obesity; 3) recent weight gain; 4) alcohol abuse; 5) pancreatic dysfunction (pancreatitis); 6) medications known to be associated with hyperglycemia. In those cases where information about a personal history of diabetes was not available, 100 reports included information about a family history of diabetes. Of these, 55% had a definite positive family history of diabetes.

Of the 419 cases hyperglycemic cases reported, 413 had interpretable measurements of plasma glucose. Sixty three of these cases had plasma glucose levels of >126 to <300 mg/dl without acute hospitalization or acidosis, 92 subjects had plasma glucose levels of >300 to <600 mg/dl without acute hospitalization or acidosis, 147 subjects had plasma glucose levels of >600 mg/dl and/or severe hyperglycemic presentation with hospital/ICU admission and/or acidosis, and peak plasma glucose was unknown in 117 subjects.

Recent reports have described cases of hyperglycemia (including cases of diabetic ketoacidosis, type 1 DM and/or type 2 DM) observed with subjects on olanzapine therapy in a total of 16 subjects (Goldstein et al. 1999; Gatta et al. 1999; Ober et al. 1999; Lindenmayer and Patel 1999; Hayek et al. 1999; Zung et al. 1999; Wirshing et al. 1998; Fertig et al. 1998). Twelve of the cases occurred in male subjects, 12 were reported as being obese, and 4 were African-Americans. Further, in five cases the subject had a family history of DM (Goldstein et al. 1999; Wirshing et al. 1998). In one case report, the hyperglycemia required insulin therapy, resolved after olanzapine was discontinued without anti-diabetic medication, and recurred upon rechallenge (Fertig et al. 1998). Another case report involved a subject with a 4-year history of diabetes (controlled by diet) and hypertension who was switched from thioridazine to olanzapine and experienced a 25% increase in weight (Ober et al. 1999). An additional case involved a 12.5-year-old subject that presented with diabetic ketoacidosis and was treated with insulin (Zung et al. 1999). Olanzapine was discontinued with no decrease in insulin requirements. Olanzapine was re-started and the subject's blood glucose levels have been mostly in the normal range over the last 6 months with a decrease in daily insulin requirements. The authors concluded that the temporal association of developing type 1 DM with olanzapine was a coincidental finding. On the basis of these case studies, it appears as though subjects that may develop hyperglycemia in temporal association with olanzapine are subjects that are typically at risk for type 2 DM based on race, obesity, or family history. It is unclear at this point whether or not the number of cases of olanzapine in temporal association with DM exceeds the expected incidence for the development of type 2 DM in subjects with schizophrenia.

Glucose homeostasis is regulated by a number of classic hormone and neurohumoral molecules, including insulin, glucagon, glucocorticoids, catecholamines, insulin-like growth factor-1 and -2, and several incretin hormones (for example, glucagon-like peptide-1). These hormones regulate hepatic, muscle, and adipose uptake and release of glucose and hepatic synthesis of glucose or glycogen. The secretion of the various

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molecules that regulate glucose concentrations are themselves under complex regulation. There is evidence that the uptake of glucose by muscle and adipose, the two tissues responsible for a significant portion of whole body glucose utilization, is affected by hormonal, neural, nutritional, and vascular factors {Reaven 1995 #111}. Changes in these factors can lead to significant changes in the responsiveness of muscle and adipose to glucose regulatory hormones, leading to insulin resistance. The mechanism by which olanzapine may be associated with hyperglycemia is speculative, however several of the clinical features of the presentation can give some insight into potential etiologic mechanisms, if olanzapine is pharmacologically linked to hyperglycemia. Among these mechanisms are weight-gain associated increase in insulin-resistance, direct effect on increasing insulin-resistance in muscle or adipose, stimulation of hepatic glucose production either directly or indirectly through neurohormonal effects, or inhibition of insulin release.

Although olanzapine-associated weight gain has been well established, it is unlikely that weight gain independent of other factors is the proximate cause of new-onset hyperglycemia. It has been shown that even small increases in weight can significantly worsen glycemic control in subjects with diabetes and can lead to overt diabetes in subjects with impaired glucose tolerance or impaired fasting glucose {Colditz 1990 #813; Chan 1994 #806; Ford 1997 #847}. However, the clinical presentation of olanzapine-associated precipitation of new-onset diabetes covers a range of mild exacerbation of pre-existing diabetes through life-threatening, hyperglycemia-induced hyperosmolar coma. No cases of weight-gain induced hyperosmolar coma have been reported in the literature.

The possibility that hyperglycemia is caused by an inhibition of insulin secretion is supported by the observation of a significant number of cases of hyperosmolar coma. Such cases are not expected to occur from either increases in weight or insulin resistance per se. It is believed that in most cases of hyperosmolar coma, a defect in insulin secretion overlays some baseline characteristics that put subjects at risk for this disorder {Fishbein 1995 #1408; Siperstein 1992 #1407; Genuth 1997 #1404; Lorber 1995 #1405}. However, this mechanism alone does not explain the cases of mild increases in glucose. In order to explore the hypothesis that atypical antipsychotics alter insulin secretion primarily, a study is now underway using the hyperglycemic clamp technique to measure pancreatic insulin secretion to a glucose load in healthy subjects. That technique approximates, but does not assess directly, insulin sensitivity at glucose concentrations in the normal or near-normal range.

This study seeks to test the hypothesis that olanzapine and risperidone impair insulin sensitivity in lean and overweight subjects. This will be determined by using a two-step euglycemic clamp (referred to hereinafter as euglycemic clamp). By means of a simultaneous infusion of both insulin and glucose, the sum of the rate of both glucose uptake and disposal can be measured at different ambient insulin concentrations but always at euglycemic conditions. The uptake and clearance of glucose can be related to

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the circulating insulin concentrations over steady state conditions thereby describing an index of insulin sensitivity.

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