

Evaluating the Effect of 8-Week Treatment With Risperidone On Fasting Blood Glucose of Patients with Schizophrenia

Hossein Khalili, ParmD¹
Simin Dashti-Khavidaki, ParmD¹
Hadi Okhvatpoor¹
Firouzeh Raesi, MD^{2,3}
Padideh Ghaeli, PharmD^{2,3}

1 Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

2 Department of Psychiatry, Tehran University of Medical Sciences, Tehran, Iran

3 Psychiatry & Psychology Research Center, Tehran University of Medical Sciences, Tehran, Iran

Corresponding author:

Hossein Khalili,
Assistant Professor, Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences Tehran, 14174, Iran.

E-mail: khalilih@tums.ac.ir

Tel: +98-912-247-1998

Fax: +98-21-66461178

Objective: This study was designed to evaluate the effects of risperidone on fasting blood glucose (FBG) in patients with Schizophrenia.

Method: Seventy five non-diabetic patients with Schizophrenia (based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria) entered this cross-sectional study. Patients did not receive any medications (Including risperidone) affecting serum FBG levels for at least 2 weeks prior to the initiation of the study. Patients received the mean dose of 4.5mg (range 2-12mg) risperidone for 8 weeks. Pregnant women, patients with diabetes mellitus and a history of any major heart disease were excluded from this study. Additionally, none of the patients should have received electroconvulsive therapy within 6 months prior to the initiation of the antipsychotics. FBG levels were measured at the initiation and 8 weeks after starting risperidone.

Results: Fifty one patients completed the study. The mean FBG level was increased from 88.9mg/dL (baseline) to 94.4 mg/dL at week 8 ($P = 0.003$). This 8-week study showed that FBG levels may increase in schizophrenic patients receiving risperidone.

Conclusion: Measuring and monitoring FBG before the initiation and during the treatment with risperidone is suggested.

Key Words:

Blood glucose, Risperidone, Schizophrenia

Iran J Psychiatry 2007; 2: 124-126

Beginning in 1990, a new generation of antipsychotic medications was introduced. These "atypical" antipsychotic medications, in comparison with the first-generation (or "conventional") antipsychotics, have been associated with improved efficacy in treating both positive and negative symptoms of schizophrenia and have exhibited a superior safety profile in adverse events such as extrapyramidal symptoms (1, 2). In the past decade, atypical antipsychotics such as risperidone, olanzapine, ziprasidone and quetiapine have become first-line treatment options for patients with schizophrenia. However, clinicians have encountered benefits as well as a host of side effects in these patients' population. Weight gain and development or exacerbation of diabetes mellitus (DM) are among serious issues that have forced clinicians to vigilantly follow up their patients' metabolic profile to prevent serious consequences (3).

Recently, the results of several case reviews and database studies have examined a potential association between atypical antipsychotic use and increased

insulin resistance or risk of developing overt diabetes mellitus (4-12). The design of these studies varied greatly with regard to their study populations, methods, results, magnitude of identified risk, and implication of specific atypical medications when compared to former studies.

Our study was designed to evaluate the effects of risperidone on fasting blood glucose (FBG) in non-diabetic patients who suffered from schizophrenia.

Materials and Methods

Seventy five non-diabetic adult patients with schizophrenia (based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria) entered this cross-sectional study. Sixty patients complied with the study criteria and completed the study. Subjects were between 19 to 65 years of age. Patients did not receive any medications or any other antipsychotic (s) that could affect serum FBG levels (eg, corticosteroids, beta-blockers, sulfonyleurea, insulin, metformin, antidepressant, etc) for 2 weeks prior to the initiation of the study and during the study.

Patients with diabetes mellitus, a history of myocardial infarction and other heart diseases, and pregnant women were excluded from the study. Additionally, none of the patients should have received electroconvulsive therapy within 6 months before the initiation of the antipsychotics. Patients received oral risperidone (2 to 12 mg/d) for 8 weeks.

FBG levels were measured at the initiation of the study as well as 8 weeks after starting risperidone. Paired samples t-test was performed for the FBG changes from the baseline. Results are presented as mean±standard error. Differences were considered significant when $P < 0.05$.

Results

Thirty four males and 17 females completed the study. The mean FBG level was increased from 88.9 ± 11.44 mg/dl (baseline) to 94.4 ± 17.04 mg/dl at week 8. The FBG levels at week 8 were significantly different from the baseline FBG levels ($P=0.003$). In males, the FBS levels were increased from 90.35 ± 11.45 mg/dl to 97.12 ± 16.86 mg/dl, ($p=0.003$) after 8 weeks treatment with risperidone, however, the increase in FBS levels from 86.24 ± 10.72 mg/dl to 88.88 ± 14.65 mg/dl was not significant in women.

The patients Body Mass Index (BMI) increased from 22.21 ± 4.21 kg/m² to 22.9 ± 4.00 kg/m² ($p=0.001$) after 8 weeks. BMI increase in males (21.71 ± 3.48 to 22.41 ± 3.38 kg/m²) was significant ($p=0.001$), but this index did not increase significantly in women (23.17 ± 5.34 to 23.86 kg/m²).

Correlation ($r=0.85$ and $p=0.03$) exists between BMI and FBS at week 8 in the male sex but not in the female sex, however, the male sex was not a risk factor for hyperglycemia (OR= 0.65, CI=0.2-1.1).

Additionally, analysis of the data showed that the increases in FBG levels did not depend on age and the dose of risperidone.

Discussion

Koller and colleagues have reported data from the U.S (13). Food and Drug Administration's MedWatch surveillance program that implicated clozapine, olanzapine, risperidone, and quetiapine may cause new-onset diabetes mellitus, including diabetic ketoacidosis.

This study on non-diabetic schizophrenic patients noted a statistically significant increase in FBG serum levels after an 8-week treatment with risperidone. The change in FBG levels are within the normal range and seem not to be clinically significant. However, these changes can become clinically important in patients with borderline FBG levels or in those with risk factors for developing diabetes (i.e., family history of diabetes and obesity).

The mechanism by which atypical antipsychotic drugs cause diabetes and other metabolic disturbances is not fully understood mainly because schizophrenia itself plays a role in the development of diabetes. However, the proposed mechanisms are; weight gain, insulin

resistance, increase in leptin concentration and glucose transport impairment (14).

The authors suggest that the FBG levels of patients with a high risk to develop diabetes and of those with borderline FBG should be considered before starting them on risperidone. Furthermore, regular monitoring of the FBG levels in these patients after initiating the atypical antipsychotic may prevent further complications. It is also very important to consider coexisting medical conditions and any drug-drug interaction before initiating risperidone.

In general, it is suggested that risperidone may be preferred over other atypical antipsychotic such as clozapine and olanzapine for use in schizophrenic patients with high normal FBG or in individuals with high risk to develop diabetes (15). Further, studies are needed to assess the effects of chronic use of risperidone on FBS levels in nondiabetic, psychotic patients.

It should also be noted that the number of the followed patients and the duration of this study was not long enough to show the chronic effects of the studied antidepressants on FBG. Also it is recommended that GTT (Glucose Tolerance Test) be considered for patients with increased FBG following the treatment with risperidone.

Acknowledgement

This research has been supported by Tehran University of Medical Sciences.

References

1. Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *Br Med J* 2000; 321: 1371-1376.
2. Tran PV, Dellva MA, Tollefson GD, Beasley CM, Potvin JH, Kiesler GM. Extrapyramidal symptoms and tolerability of olanzapine versus haloperidol in the acute treatment of schizophrenia. *J Clin Psychiatry* 1997; 58: 205-211.
3. Gianfrancesco FD, Grogg AL, Mahmoud RA, Wang R, Nasrallah HA. Differential Effects of Risperidone, Olanzapine, Clozapine, and Conventional Antipsychotics on Type 2 Diabetes: Findings From a Large Health Plan Database. *J Clin Psychiatry* 2002; 63: 920-930.
4. Jin H, Meyer JM, Jeste DV. Phenomenology of and Risk Factors for New-Onset Diabetes Mellitus and Diabetic Ketoacidosis Associated with Atypical Antipsychotics: An Analysis of 45 Published Cases. *Ann Clin Psychiatry* 2002; 14: 59-64.
5. Koller E, Schneider B, Bennett K, Dubitsky G. Clozapine-associated diabetes. *Am J Med* 2001; 111: 716-723.
6. Koller EA, Doraiswamy PM. Olanzapine-Associated Diabetes Mellitus. *Pharmacotherapy* 2002; 22: 841-852.

7. Koro CE, Fedder DO, L'Italien GJ, Weiss SS, Magder LS, Kreyenbuhl J, et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *Br Med J* 2002; 325: 243.
8. Lund BC, Perry PJ, Brooks JM, Arndt S. Clozapine Use in Patients With Schizophrenia and the Risk of Diabetes, Hyperlipidemia, and Hypertension A Claims-Based Approach. *Arch Gen Psychiatry*, 2001; 58: 1172-1176.
9. Meyer JM. A retrospective comparison of weight, lipid, and glucose changes between risperidone-and olanzapine-treated inpatients: metabolic outcomes after 1 year. *J Clin Psychiatry* 2002; 63: 425-433.
10. Mohan D, Gordon H, Hindley N, Barker A. Schizophrenia and diabetes mellitus. *Br J Psychiatry Suppl* 1999; 174: 180b.
11. Sernyak MJ, Leslie DL, Alarcon RD, Losonczy MF, Rosenheck R. Association of Diabetes Mellitus With Use of Atypical Neuroleptics in the Treatment of Schizophrenia. *Am J Psychiatry* 2002; 159: 561-566.
12. Wirshing DA, Wirshing WC, Kysar L, Berisford MA, Goldstein D, Pashdag J, et al. Novel antipsychotics: Comparison of weight gain liabilities. *J Clin Psychiatry* 1999; 60: 358-363.
13. Koller EA, Cross JT, Doraiswamy PM, Malozowski SN. Pancreatitis Associated with Atypical Antipsychotics :From the Food and Drug Administration's MedWatch Surveillance System and Published Reports. *Pharmacotherapy* 2003; 23: 1123-1130.
14. Chue P. The Assessment and Management of Antipsychotic-Associated Metabolic Disturbances from a Psychiatric Perspective. *Can J Psychiatry* 2004; 49: 200-207.
15. Lindenmayer JP, Czobor P, Volavka J, Citrome L, Sheitman B, McEvoy JP, et al. Changes in Glucose and Cholesterol Levels in Patients With Schizophrenia Treated With Typical or Atypical Antipsychotics. *Am J Psychiatry* 2003; 160: 290-296.