A Case of Diabetic Ketoacidosis Associated with Risperidone Treatment

Risperidon Tedavisi ile İlişkili Diyabetik Ketoasidoz Vakası

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Abstract
The association between schizophrenia and diabetes has been previously documented. Case reports have also demonstrated that initiation of atypical antipsychotic agents may induce or exacerbate diabetes mellitus.
A 26-year-old man without a family history of diabetes mellitus presented with deep coma after 5 months of treatment with risperidone. He was diagnosed with diabetic ketoacidosis, was given insulin and saline infusion, and his antipsychotic agent was changed from risperidone to ziprasidone. Insulin therapy and oral agent was discontinued within two months of follow-up. The rapid onset of diabetes, and the disappearance of hyperglycemia after discontinuation of the drug suggested that risperidone had been a factor in his diabetic ketoacidosis.
During three years of subsequent follow-up, testing revealed no evidence of elevated serum glucose levels or impaired glucose tolerance.
In our opinion psychiatrists should routinely ask patients treated with antipsychotic agents such as risperidone for diabetic symptoms, weight loss, lethargy, polydipsia and/or polyuria, and monitor serum glucose levels. Although there is no consensus on the best way to switch from one antipsychotic drug to another, for those patients who develop diabetes during therapy with risperidone a change to ziprasidone treatment may maintain normal glucose levels. *Turk Jem 2008; 12: 97-8*
Keywords: Risperidone, diabetes mellitus, ziprasidone

Özet
Şizofreni ile diyabet arasındaki ilişki daha önceden bilinmektedir. Buna ilaveten bazı vaka takdimlerinde antipsikotik ajanların diyabet gelişimini veya diyabetin şiddetini arttırabildiği gösterilmiştir.
5 aydır risperidon tedavisi alan ve ailesinde diyabet öyküsü olan 26 yaşında erkek hasta ağır koma bulguları ile başvurdu. Diyabetik ketoasidoz teşhisi konan olgu insülin ve izotonik sodyum klorür infüzyonu takiben risperidon tedavisi ziprasidon tedavisi ile değiştirildi.
İnsülin tedavisi ve oral antidiyabetik ilaç iki aylık takibi esnasında kesildi. Hızlı bir şekilde ortaya çıkan diyabet, ve risperidon kullanımının kesilmesinden sonra hipergliseminin ortadan kaybolması hastanın diyabetik ketoasidozunun risperidon kullanımına bağlı olabileceğini düşündürmüştür.
3 yıllık takip esnasında hastanın kan şekerleri aralıklı olarak OGTT ile kontrol edilmiş ve takipler esnasında hastada ne bozulmuş açlık glukozu ne de bozulmuş glukoz toleransı tespit edilmiştir.
Bizim düşüncemize göre psikiyatrist meslektaşlarımızın hastalarında risperidon kullanımı esnasında diyabetik semptomlar bunlar arasında kilo kaybı, letarji, çok su içme ve/veya çok idrara çıkma şikayeti açısından hastalarını sorgulamaları ve kan şeker kontrollerini rutin olarak yaptırmaları gerekmektedir.
Her ne kadar antipsikotik ajanların birbirleri ile değişimleri açısından tam bir görüş birliği olmasa da, risperidon kullanımı esnasında ortaya çıkan diyabette, risperidon yerine ziprasidon kullanarak kan şekeri kontrol altına alınabilinir. *Turk Jem 2008; 12: 97-8*
Anahtar kelimeler: Risperidon, diyabet, ziprasidon

Introduction

There is evidence to suggest that atypical antipsychotic medications can increase the risk of diabetes mellitus (1,2). Cases have ranged in severity from mild glucose intolerance to hyperosmolar coma or diabetic ketoacidosis, a rare but potentially fatal metabolic complication (2,3). In these reports, most cases of new-onset disturbances of glucose homeostasis improved after changing antipsychotic medication. However, there is no consensus on the best way to change from one antipsychotic drug to another. A successful

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Turkish Journal of Endocrinology and Metabolism, published by Galenos Publishing. All rights reserved.

approach may be gradual discontinuation of the current antipsychotic drug and immediate initiation of the new treatment (4). According to recent reviews, the risk of diabetes is highest for clozapine and olanzapine, followed by quetiapine and risperidone, and lowest for those receiving ziprasidone treatment (2,5).
Given these limited data, a strong causal association is indicated between the use of risperidone and hyperglycemia. This may help to reinforce the concept that this agent may precipitate diabetic ketoacidosis. Ziprasidone treatment does not appear to contribute to these metabolic abnormalities.

Case Report

The patient was a 26-year-old male with a long-standing history of schizophrenia with poor medication adherence, resulting in frequent hospitalizations. After five months of treatment with risperidone (6 mg daily), he was noted to be confused and lethargic and was admitted to our emergency department. On admission, height was 177.0 cm and weight was 93 kg, BMI=31 kg/m^2, pulse rate was 110 beats/min, and blood pressure was 95/75 mm Hg. Laboratory investigation revealed a random glucose of 338 mg/dL and a glycosylated hemoglobin of 11.2%. Homeostasis model assessment (HOMA) index was calculated 4.04. Biochemical evaluation suggested metabolic acidosis with ketonemia (pH: 7.23, sodium 127, chloride 92, 3+ by reagent strip testing). The patient was diagnosed with diabetic ketoacidosis.
The patient was emergently admitted to the intensive care unit and treated with aggressive intravenous hydration and insulin infusion. On his return to the psychiatric inpatient unit, it was decided to discontinue risperidone treatment and switch to ziprasidone (80 mg daily) for management of schizophrenic symptoms. Autoantibodies to GAD65 or IA-2 were negative in our patient. Intravenous administration of insulin was replaced by intermittent subcutaneous administration; serum glucose was maintained in a normal range by dietary therapy alone (25 kcal/kg/day) within two months. In three years of subsequent follow-up, oral glucose tolerance tests were used to assess changes in glucose levels; neither impaired glucose tolerance nor high levels of fasting plasma glucose was observed. The patient's lipid profile and weight did not change during ziprasidone treatment.

Discussion

Schizophrenia is a risk factor for new-onset type 2 diabetes. The causative factors are partly explained by obesity, cigarette smoking, physical inactivity, and insulin resistance (6-8). There is also evidence to suggest that atypical antipsychotics can increase the risk of diabetes mellitus (1,2). Diabetic ketoacidosis is one of a spectrum of metabolic disorders that have been linked to the use of atypical antipsychotic agents (2,3).
The mechanism by which the atypical antipsychotics cause hyperglycemia remains unclear. The ability of various drugs in this class to cause hyperglycemia varies. Case reports of adverse effects on glucose and lipid metabolism (for example, type 2 diabetes mellitus and dyslipidemia) have more frequently and consistently been associated with clozapine and olanzapine treatment than with quetiapine or risperidone treatment (2,5).
In our case, rapid development of uncontrolled diabetes with metabolic acidosis, disappearance of hyperglycemia after discontinuation of risperidone, and lack of recurrence with ziprasidone treatment suggest that the development of diabetes in this patient was a risperidone-related effect. Case studies have shown a significantly greater risk of hyperglycemia with risperidone than with ziprasidone treatment.
We searched cases of risperidone-associated diabetes or hyperglycemia in the literature for information of the effect of drug dosage. Dosages ranging from 0.5-12 mg/day were found. The mean±SD dosage of 4.7±2.5 mg/day was the same for new-onset patients and those with preexisting diabetes. There was no correlation between dosage and time to onset.
The finding of our report is consistent with the evidence Melkersson and Leslie et al. (2,5)-that any condition that increases hyperglycemia with antipsychotic treatment may require switching to ziprasidone to control metabolic abnormalities. Metabolic abnormalities may also be improved by weight loss and reduced BMI in patients switching from risperidone to ziprasidone (8). Kingsbury et al. reported that a six-week trial of ziprasidone appeared to lead to significant reduction of serum cholesterol and triglyceride levels (9). This finding may mean that ziprasidone does not increase cholesterol or triglycerides, or that the decrease was related to the withdrawal of other atypical antipsychotic drugs that had initially increased cholesterol and triglycerides. In the present case, after changing from risperidone to ziprasidone, the patient's body weight and lipid profile were unchanged, but significant improvements in glucose metabolism were noted in follow-up. This may be related to ziprasidone's unique combination of relatively low histamine H1 affinity and potent serotonin 5-HT1A agonist activity, which may be responsible for its lower propensity to cause abnormalities in glucose-insulin homeostasis (10).
For those patients who develop diabetes during therapy with risperidone treatment, change of treatment to another antipsychotic agent may be the first recommendation. The patient should be followed for weight, fasting blood glucose, and fasting serum concentrations of insulin and lipids before initiation of treatment and then at regular intervals during such antipsychotic treatments.

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