

DIABETES MELLITUS ASSOCIATED WITH SECOND GENERATION ANTIPSYCHOTICS: TWO CASE REPORTS AND REVIEW OF THE LITERATURE

Bojana Maksimović, Ivana Pavlić-Renar, Željko Metelko

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be at an increased risk of developing diabetes and should be tested for glycemc abnormalities regardless of whether or not receiving antipsychotic medication.

SUMMARY

Atypical antipsychotics have a lower incidence of extrapyramidal side effects while possibly improving cognitive and mood symptoms. Many literature case reports and studies have pointed to their possible diabetogenic effect. Much debate has been focused on whether it is characteristic of the whole class of drugs or of some specific agent. Moreover, the possible relationship of psychoses per se and diabetes has not been ruled out. We report on two cases of new onset diabetes mellitus in patients treated with second generation antipsychotics: a 40-year-old man treated with a combination of two atypical antipsychotics, aripiprazole and quetiapine, who suddenly developed diabetes mellitus, and a 29-year-old man treated with risperidone who developed diabetes mellitus with ketoacidosis. This is in line with prospective studies which have demonstrated an association of all atypical antipsychotics with impaired glucose metabolism but without a convincing evidence for a causal relationship or any difference between particular agents. Well-designed interdisciplinary prospective studies are needed to clarify the issue. In addition, patients with schizophrenia might

INTRODUCTION

The modern era in the treatment of psychotic disorders began in 1952 with the discovery of chlorpromazine. Initially, chlorpromazine and other drugs from this group were called neuroleptics because of the extrapyramidal symptoms they produced. A more appropriate label for this entire drug class is "antipsychotic medication", first generation for the chlorpromazine group, and second generation for the clozapine group, also known as atypical antipsychotics (1).

In the mid-1960s, an association between diabetes and first generation antipsychotics was reported (2), however, later data provided evidence for an even higher risk for second generation antipsychotic drugs. Second generation antipsychotics (SGAs) are important in the management of many psychiatric conditions. The currently available evidence indicates that SGAs have significant effects in reducing the positive symptoms of schizophrenia. They also appear to improve the negative symptoms and cognitive difficulties that are prominent in patients treated with first generation antipsychotics and to have a lower incidence of extrapyramidal side effects as compared to

Correspondence to: Ivana Pavlić-Renar, M.D.,PhD, Vuk Vrhovac University Clinic, Dugi Dol 4a, HR-10000 Zagreb, Croatia
E-mail: ivana@idb.hr

first generation antipsychotics (FGAs) (1). Since the introduction of these medications over the last decade, starting with clozapine in 1989, several case reports in the literature have suggested that they might be associated with weight gain, new onset diabetes mellitus, and disturbances of lipid metabolism.

We present case reports of two patients treated with SGAs who developed new onset diabetes mellitus and new onset diabetes mellitus with ketoacidosis: a 40-year-old man treated with a combination of two atypical antipsychotics, aripiprazole and quetiapine, who suddenly developed diabetes mellitus; and a 29-year-old man treated with risperidone who developed diabetes mellitus with ketoacidosis. Similar cases were found in the literature by MEDLINE assisted search using the key words “diabetes mellitus”, “atypical antipsychotics”, and “adverse drug effects”.

CASE REPORTS

Case 1

A 40-year-old male Caucasian with a family history of diabetes mellitus (father and uncle) and 7-year duration of schizoaffective psychosis was admitted to emergency diabetology service for rapid weight loss, polydipsia and polyuria. On admission, his medication included aripiprazole, quetiapine, valproic acid, carbamazepine and diazepam. He smoked three packs of cigarettes *per* day, and denied any use of alcohol and illicit drugs. His symptoms appeared three months prior to examination, roughly from the time of the introduction of aripiprazole as an add-on drug to previous quetiapine monotherapy.

On physical examination, his body height was 186 cm and body weight 77 kg; body mass index (BMI) 22.6 kg/m²; blood pressure 110/60 mm Hg, and heart rate 90/min. Heart and lung examination revealed no abnormalities. The abdomen was tender, with hepatomegaly of approximately 2 cm. Distal pulses were palpable, and there was no peripheral edema. There were no focal neurological deficits.

Blood glucose was 35.3 mmol/L; other laboratory values were as follows: sodium 133 mmol/L, potassium 4.1 mmol/L, creatinine 106 μmol/L, calcium 1.05 mmol/L, chloride 91 mmol/L, serum osmolality 290 mosm/kg, capillary blood pH 7.42, bicarbonates 25.8 mmol/L, base excess -1.3 mmol/L, oxygen saturation

95.2, white cell count 6.2x10⁹/L, hematocrit 0.437 l/L, hemoglobin 159 g/L, and platelets 124x10⁹/L; urine deep stick was positive for ketones and glucose. Hemoglobin A1c was not measured at the time of admission.

His condition was diagnosed as diabetes mellitus. Hyperglycemia and electrolyte disbalance (hyponatremia and hypocalcemia) were regulated with insulin drip in 0.9% NaCl with intravenous substitution of calcium. He was released with two doses of premixed insulin and intensive basal-bolus insulin regimen a few days later. His next visit occurred three months later. The patient was no longer on insulin treatment, which had been gradually discontinued and normoglycemia maintained. The antipsychotic regimen was still the same. Laboratory findings at the time of this second visit were as follows: blood glucose 4.0 and postprandial glucose 5.8 mmol/L, hemoglobin A1c 5.55%, creatinine 89 μmol/L, electrolyte values within the normal range, slightly increased triglycerides, and normal values of total cholesterol, LDL and HDL in the lipidogram. Also, the values of insulin and C-peptide were measured before and after the meal, to show a satisfactory level of endogenous insulin. Islet-cell autoantibodies (ICA) were 0.5 (intensity of fluorescence) and glutamic acid decarboxylase autoantibodies (GADA) were negative, probably excluding diabetes mellitus type 1.

On his third visit 7 months later, normoglycemia was still maintained, without any specific medicamentous or dietetic intervention, HbA1c was 5.67%, and blood glucose measurements were within the normal range. At that time his antipsychotic medication had been discontinued for five months and he was only receiving diazepam.

Case 2

A 29-year-old male Caucasian with no family history of diabetes mellitus and 7-year duration of schizophrenia was admitted to diabetology emergency service for nausea and vomiting. The symptoms occurred 7 days before with malaise, nausea, abdominal pain, polydipsia and polyuria. His medical history was notable for ulcerous colitis in his early childhood. His medications were risperidone and promazine. The time of this therapy initiation was unknown.

He smoked two packs of cigarettes *per* day and denied any use of alcohol and illicit drugs.

On physical examination, his body height was 184 cm, body weight 128 kg, and BMI 37.81 kg/m²; blood pressure was 140/90 mm Hg and heart rate 124/min. Heart and lung examination revealed no abnormalities; abdomen was tender with no organomegaly or diffuse pain on palpation. Distal pulses were palpable, and there was no peripheral edema. There were no focal neurological deficits.

His blood glucose was 30.3 mmol/L; other laboratory values were as follows: sodium 136 mmol/L, potassium 6.0 mmol/L, creatinine 135 μmol/L, AST 66 U/L, ALT 133 U/L, serum amylase 97 U/L, capillary blood pH 7.236, bicarbonate 5.2 mmol/L, base excess -22.5 mmol/L, oxygen saturation 96%, white cell count 10.90x10⁹/L, red cell count 5.55x10¹²/L, hematocrit 0.483 l/L, hemoglobin 164 g/L, platelets 256x10⁹/L, hemoglobin A1c 12.90%, and no lipidogram abnormalities, blood ketones were high. Urine deep stick was positive for ketones, glucose, protein and red cells.

He was admitted for hospital treatment and his condition was diagnosed as diabetic ketoacidosis. Insulin drip and intravenous fluid resuscitation were introduced. His nausea and vomiting resolved overnight and his blood glucose normalized. After achieving normoglycemia intensive basal-bolus insulin regimen was started. The patient took part in diabetes and dietary education, and was released from the hospital 9 days after admission.

ICA and GADA autoantibodies were both negative, making it unlikely that patient had autoimmune type 1 diabetes mellitus. On control visit 10 days after his discharge from the hospital his blood glucose measurements were within the normal range. His antipsychotic medication remained the same. After that he was lost for control.

DISCUSSION

The second generation antipsychotics include clozapine, risperidone, olanzapine, quetiapine and aripiprazole. Introduced first with clozapine in 1990, they have been widely prescribed.

SGAs have a lower incidence of extrapyramidal side effects, and improve cognitive and mood symptoms (1). Four years later, in 1994, Kamran *et al.* published the first case report associating the use of clozapine in a psychotic patient with new onset diabetes mellitus (3).

We searched through MEDLINE database across the 11-year period of SGA use and found 85 case reports on new onset diabetes mellitus in patients who received SGAs for their psychiatric condition (4-34), including our two case reports. The incidence of new onset diabetes mellitus according to particular SGAs is shown in Table 1.

Table 1. Cases of new onset diabetes mellitus according to second generation antipsychotics

Drug	No. of new onset DM cases
Clozapine	27
Olanzapine	47
Risperidone	4
Quetiapine	4
Aripiprazole	1
Ziprasidone	0
Total	83

Literature data show that patients younger than 50 were involved in 80% of cases (35), the youngest being aged 7 and the oldest 75 (31,32). In 85 case reports there were 6 deaths from diabetic ketoacidosis (7,25,27,34).

In his overview of the literature from 1996 to 2001, Cohen analyzed different studies, most of them indicating an elevated risk of diabetes mellitus development with clozapine and olanzapine (35). Sernyak *et al.* report on the results of a large retrospective study in a total of 38,632 patients receiving prescriptions for atypical and typical neuroleptics. They compared the prevalence of diabetes mellitus among these patients and found the patients who received atypical neuroleptics to be by 9% more likely to develop diabetes mellitus than those who received typical neuroleptics, while the prevalence of diabetes was significantly increased in patients who received clozapine, olanzapine and quetiapine but not risperidone (36).

Table 2. **Second generation antipsychotics and metabolic abnormalities**

Drug	Weight gain	Risk of diabetes	Lipid profile worsening
Clozapine	+ + +	+	+
Olanzapine	+ + +	+	+
Risperidone	+ +	D	D
Quetiapine	+ +	D	D
Aripiprazole*	+ / -	-	-
Ziprasidone*	+ / -	-	-

* new drugs with limited long-term data; + = increase effect; - = no effect; D = discrepant results

Adapted from: Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. Diabetes Care 2004;27:596-601.

The six currently available SGAs vary in their efficacy, formulation, biochemistry, receptor binding, and side effect profiles (37). Clozapine is the most effective antipsychotic but is only indicated after other medications have failed or in patients at a high risk of suicidal behavior, largely because it can cause agranulocytosis (37)

The most common metabolic disturbances associated with SGAs are weight gain, glucose metabolism abnormalities, and lipid profile worsening (38). There is considerable evidence, particularly in patients with schizophrenia, that treatment with SGAs can cause rapid increase in body weight. There is variability in weight gain among various SGAs (Table 2).

Time period for clinical manifestation of diabetes mellitus varies from four days to four years of the introduction of SGA medication (19,33).

Several mechanisms have been discussed to be involved in the antipsychotic-induced glucose dysregulation: opposite effects of serotonin receptors on glucose homeostasis, antipsychotic-induced obesity which is thought to be the result of antihistaminergic and antiserotonergic effects, possible beta-cell toxicity, insulin resistance, and the role of prolactin in the dysregulation of glucose metabolism (38-40).

Because of the lack of well-designed prospective studies and meta-analysis, a Consensus Development Conference on Antipsychotic Drugs, Obesity and Diabetes was held in November 2003. The international group of diabetologists and psychiatrists met to create guidelines for the management of diabetic risk in patients with severe mental illness.

On the basis of available data, it was concluded that there was an increased risk of obesity, diabetes and dyslipidemia in patients treated with SGAs. The etiology is uncertain and it is unclear whether

psychiatric condition *per se* accounts for this increased prevalence (37). They concluded that clozapine and olanzapine were associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia; risperidone and quetiapine with an intermediate effect; and aripiprazole and ziprasidone with little or no significant risk of weight gain and diabetes mellitus (37).

In 2005, a paper by Holt *et al.* gave a different perspective and conclusions. They analyzed the link between diabetes and schizophrenia. They noted that literature data were consistent in reporting a diabetes prevalence rate of around 15% in the population with schizophrenia, which is a two- to three-fold risk in the general population (41). Subramaniam *et al.* studied 194 patients with schizophrenia and report on the overall prevalence of diabetes and impaired glucose tolerance in these patients of 16% and 30.9%, respectively, which is higher than in the general population (42). Holt *et al.* also noted that the high prevalence of diabetes in people with schizophrenia was observed prior to any antipsychotic treatment, suggesting that schizophrenia itself might be an independent risk factor for diabetes, that the role of antipsychotic medication in the development of diabetes is controversial and that the attributable risk is low (41).

The case reports presented above are in line with other studies which have demonstrated the association of SGAs with metabolic disturbances, yet without convincing evidence for a causal relationship or difference between the agents. Well-designed interdisciplinary prospective studies are needed to clarify the issue.

In addition, patients with schizophrenia might be at an increased risk of developing diabetes and should be tested for glycemic abnormalities regardless of whether or not they receive antipsychotic medications.

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