

Severe Diabetic Ketoacidosis Precipitated by an Atypical Antipsychotic Drug

Mohammad Naeem Niazy, MRCP, FRCPI* Ghassan Baidas, MRCP, FRCPI* Thomas
Isaac Neyyarapally, MBBS, MD** Shuja-Ud-Din, MRCP***

We report a young Kuwaiti gentleman who presented with severe diabetic ketoacidosis (DKA) associated with atypical antipsychotic drug olanzapine. The current medical literature suggests that atypical antipsychotic drugs, including olanzapine lead to weight gain, insulin resistance, impaired glucose tolerance, diabetes mellitus (DM) and rarely patient may present with serious side effects like DKA. Clinicians are urged to monitor the emergence of metabolic risk factors periodically and remain aware of potentially serious effects like DKA in schizophrenic patients taking olanzapine.

Bahrain Med Bull 2007; 29(4):

Antipsychotic medications are the mainstay of treatment for psychotic illnesses. The conventional or first generation antipsychotics (FGAs) were introduced in 1950 and are effective in treating positive symptoms of psychosis. FGAs do not, however, adequately alleviate negative symptoms (e.g., withdrawal, apathy, poverty of speech), cognitive impairment, and affective symptoms. With the introduction of the atypical antipsychotics in late 1980s, the use of these medications has soared. These newer antipsychotics have many notable benefits compared with their earlier counterparts, but their use has been associated with reports of dramatic weight gain, diabetes mellitus, even acute metabolic decompensation, e.g., DKA and atherogenic lipid profile (increased LDL cholesterol and triglyceride levels and decreased HDL cholesterol)¹. There are few reports in the literature indicating that Olanzapine, a newer antipsychotic agent, is associated with onset or worsening of pre-existing diabetes mellitus, weight gain and metabolic syndrome. However, severe DKA as a presenting manifestation is very rarely reported in the literature. Increased physician awareness about the emergence of insulin resistance metabolic syndrome and precipitation of life threatening side effects like DKA with atypical antipsychotic agents is of great importance.

The aim of this paper is to report the case of a young Kuwaiti gentleman who presented with severe diabetic ketoacidosis (DKA) associated with atypical antipsychotic drug olanzapine.

* Consultant Physician
** Registrar Internal Medicine
*** Medical Specialist
Department of Medicine
Al-Sabah Hospital, Kuwait

THE CASE

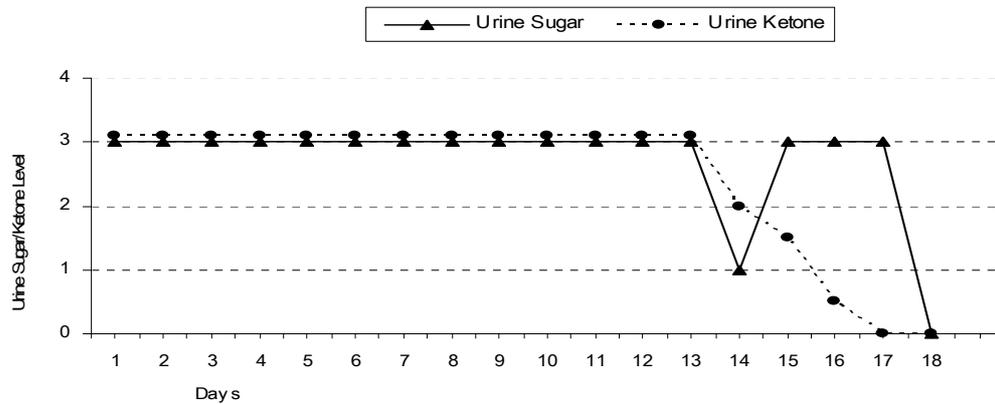
A twenty-eight year old Kuwaiti patient was diagnosed to have schizophrenia for the last 8 years. He was on conventional antipsychotic drugs, but his symptoms were not fully controlled and was therefore initiated on olanzapine eighteen months ago. There was no past and family history of diabetes mellitus, hypertension, dyslipidemia or ischemic heart disease. He was brought in a state of stupor and confusion to the emergency department and was found to be severely dehydrated. He had significant osmotic symptoms (polyuria, polydipsia) for last 20 days.

On examination, the patient was drowsy but arousable, had sinus tachycardia, tachypnoea, oxygen saturation was normal on room air. He was obese (BMI 37.7 kg/m²) and had normal BP (130/90). Systemic examination (CNS, CVS, respiratory system and abdomen) was unremarkable. Baseline investigations (table 1) demonstrated DKA. Calculated anion gap was 27.8 mmol (NR: 10-18 mmol). ECG revealed sinus tachycardia and CT brain, USG abdomen, ECHO and Chest X-ray were normal.

Table 1: Baseline blood and urinary parameters of the patient on olanzapine presenting with diabetic ketoacidosis (DKA)

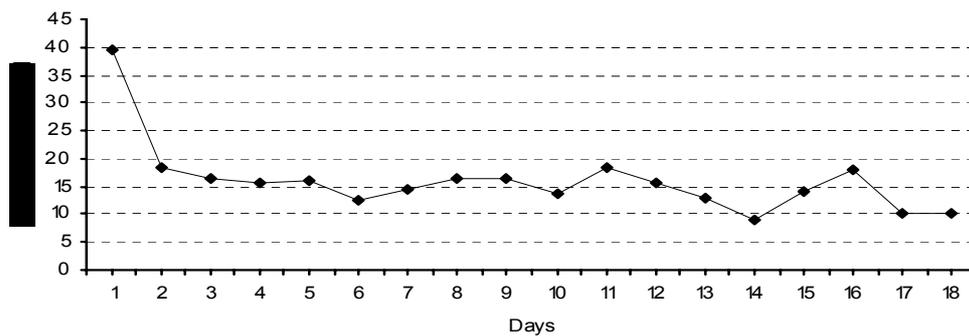
Variables	Patient value	Variables	Patient value
Blood sugar [mmol/L]	39.4	Creatinine [mmol/L]	140
Blood PH	7.219	BUN [mmol/L]	6.4
Bicarbonate [mmol/L]	7.8	Total cholesterol [mmol/L]	6.43
Potassium [mmol/L]	3.8	Triglycerides [mmol/L]	5.23
Sodium [mmol/L]	130	Uric acid [μ mol/L]	639
Chloride [mmol/L]	98.2	Lactate [mmol/L] (NR: 0.50 – 2.20)	0.92
Urine sugar	+++	WBC count [$\times 10^9/L$]	5.92
Urine Ketones	+++	D-Dimer [ng/mL]	< 250

DKA induced by olanzapine was diagnosed; he was treated with insulin, IV fluids and potassium supplements and the antipsychotic drug was stopped. Following withdrawal of olanzapine, hyperglycemia and acidosis improved gradually and ketonuria disappeared over the next seven days. He was discharged on 2 doses of insulin Mixtard. Later, in view of recurrent hypoglycemic symptoms, insulin was tapered and he was normoglycemic without insulin after one month of discharge. Olanzapine was replaced with risperidone for the treatment of his negative schizophrenic symptoms.



↓ Day Olanzapine stopped

Graph 1: This graph shows the relationship between urine sugar, urine ketones and discontinuation of Olanzapine



↓ Day Olanzapine stopped

Graph 2: This graph shows the relationship of Olanzapine with metabolic dysregulation

DISCUSSION

Data from most studies suggest that the prevalence of both DM and obesity among individuals with schizophrenia and schizo-affective disorders is 1.5–2.0 times higher than in the general population^{1,2}. In the treatment of schizophrenia, atypical antipsychotics are preferred over conventional antipsychotics due to lack of adequate response of negative symptoms and high rate of extra pyramidal side effects of conventional antipsychotics³. Atypical antipsychotic drugs especially olanzapine and clozapine have been found to induce weight gain, hypercholesterolemia, hypertriglyceridemia and DM. However, DKA is extremely rare as a presenting manifestation.

Patients developing secondary diabetes mellitus following olanzapine are about 10 years younger, than what is seen in the community⁴. The relative risk (RR) of olanzapine induced DM is 4.2 compared to the risk associated with conventional antipsychotics and 5.8 compared to those patients with no treatment⁵. Hyperglycemia and DKA related to olanzapine may occur approximately 10 days to 18 months following the initiation of the drug⁶.

The temporal relationship of secondary DM and precipitation of DKA from olanzapine is confirmed in this case as the patient became normoglycemic spontaneously after one month of cessation of the drug. Secondary DM and other metabolic abnormalities like weight gain, obesity, hyperlipidemia and hypertriglyceridemia were present in our case at the time of presentation and improved remarkably after cessation of olanzapine.

The most likely mechanism of abnormal glucose homeostasis with olanzapine and other atypical antipsychotics are probably through weight gain and obesity, mediated by central nervous system blockade of the serotonin receptor 5HT_{2C}^{7,8}. Olanzapine also induces hyperinsulinemia and insulin resistance⁹. Recent theory postulates that olanzapine has an inhibitory role in insulin secretion through potent anticholinergic activity at the islet cells of pancreas¹⁰. Although patients similar to this case revert to a euglycemic state and regression of hyperlipidemia, the negative symptoms worsen on cessation of atypical antipsychotics. It has been suggested to continue on atypical antipsychotic olanzapine with regular monitoring and control of the blood sugar with appropriate anti-diabetic treatment under the guidance of specialist¹¹.

Recent guidelines for prevention and treatment of associated risks in patients using atypical antipsychotics drugs are¹:

١. Assess patients for metabolic risks when prescribing atypical anti-psychotic agents.
٢. Educate patients, family and care givers about potential risks.
٣. Screen for baseline measurements: body mass index (BMI), waist circumference, blood pressure (BP), fasting blood glucose, fasting lipid profile. Screen before or as soon as clinically possible after prescribing the above medications.
٤. Take a personal/family history regarding obesity, diabetes, dyslipidemia, hypertension and cardio-vascular disease.
٥. Monitor: BMI at 4 and 8 weeks after initiating drug therapy, then every 6 months, waist circumference: annually; fasting plasma glucose and BP at 12 weeks then annually; fasting lipid profile at 12 weeks, then every 5 years.
٦. Refer to a specialist when appropriate.

From the above guidelines, it is clear that:

١. A close monitoring of patients on atypical antipsychotic agents is needed to monitor the emergence of metabolic risk factors such as dyslipidemia, impaired glucose tolerance, insulin resistance and diabetes.

2. Clinicians are urged to remain vigilant for various adverse effects like weight gain, impaired glucose tolerance, DM and potentially serious metabolic side effects like DKA with the use of atypical antipsychotic agents.

CONCLUSION

This case highlights the need of increased physician awareness about the serious side effect like DKA with olanzapine, an atypical antipsychotic drug.

Atypical antipsychotic drugs induce metabolic side effects like insulin resistance, weight gain, IGT/DM and rarely DKA, which needs specialist supervision.

REFERENCES

1. On behalf of the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care* 2004; 27(2):596-601.
2. Cohen D, Stolk RP, Grobbee DE, *et al.* Hyperglycemia and Diabetes in Patients with Schizophrenia and Schizoaffective Disorders. *Diabetes Care* 2006; 29(4):786-91.
3. Maria D. Llorente, Victoria Urrutia, Psychiatric Disorders and the Metabolic Effects of Anti Psychotic Medications. *Clinical diabetes* 2006; 24:18-24.
4. Koller EA, Doraiswamy PM. Olanzapine Associated Diabetes mellitus. *Pharmacotherapy* 2002; 22(7):841-52.
5. Koro CE, Fedder DO, L'Italiani GJ, *et al.* Assessment of Independent Effect of Olanzapine and Risperidone on Risk of Diabetes among Patients with Schizophrenia: Population Based Nested Case-control Study. *BMJ* 2002; (3)325:243.
6. Lindenmayer JP, Nathan AM, Smith C. Hyperglycemia Associated with the Use of Atypical Antipsychotics. *J Clin Psychiatry*. 2001; 62(23):30-38.
7. Meyer JM. A Retrospective Comparison of Lipid, Glucose, and Weight Changes at One Year between Olanzapine – and Risperidone–treated Inpatients. *Biol Psychiatry* 2002; 63(5):425-33.
8. Goldstein LE, Sporn J, Brown S, *et al.* New-onset Diabetes Mellitus and Diabetic Ketoacidosis Associated with Olanzapine Treatment. *Psychosomatics* 1999; 40:438-43.
9. Melkersson KI, Hultin AL, Brismar KE. Different Influences of Classical Antipsychotics and Clozapine on Glucose-insulin Homeostasis in Patients with Schizophrenia or Related Psychoses. *J Clin Psychiatry* 1999; 60:783-91.
10. Johnson DE, Yama Zaki H, Ward KM, *et al.* Inhibitory Effects of Antipsychotics on Carbachol–enhanced Insulin Secretion from Perfused Rat Islets: Role of Muscarinic Antagonism in Antipsychotic Induced Diabetes and Hyperglycemia. *Diabetes* 2005; 54:1552-8.
11. Howes OD, Rifkin L. Diabetic Ketoacidotic (DKA) Coma Following Olanzapine Initiation in a Previously Euglycemic Woman and Successful Continued Therapy with Olanzapine. *Journal of psycho-pharmacology* 2004; 18(3):435-7.