

Olanzapine-induced Diabetic Ketoacidosis in a Saudi Female

Hasan S Al-Amri, MD, SSC-Psych*

A twenty-seven-year-old Saudi woman with a 10-year history of bipolar affective disorder required numerous hospitalizations. On her last admission, Olanzapine (15 mg q.i.d.) and Clonazepam (2 mg bid) were initiated. Before treatment with Olanzapine, she had normal random serum glucose levels. Her body weight was 75 kg, and her body mass index (BMI) was 33.3 kg/m². On discharge, controlled-release sodium valproate (750 mg bid) was added to her regimen and Olanzapine dose was decreased to 10 mg/day. After few months, she developed progressive somnolence, polyuria, and polydipsia. Serum glucose was 800 mg/dl, and urine was positive (+3) for ketones. She was diagnosed as diabetic ketoacidosis (DKA). Her weight had increased 9 kg.

The patient was treated with intravenous fluids and insulin. She was placed on a sliding scale insulin regimen besides Metformin. Olanzapine was discontinued and replaced with Haloperidol.

Bahrain Med Bull 2009; 31(3):

Olanzapine is one of the new atypical antipsychotic medications. Structurally related to the prototype atypical antipsychotic Clozapine; Olanzapine exhibits a similar profile for receptor affinity and shares many of its behavioral, neuro-endocrine, and electrophysiological properties¹. It is highly effective for the treatment of schizophrenia, schizoaffective disorder, bipolar affective disorder, and other psychotic disorders. It has been administered to more than 20 million patients worldwide². Several cases have linked Olanzapine with impaired glucose metabolism and diabetes mellitus³⁻⁶. However, there are few reported cases of Olanzapine-induced diabetic ketoacidosis^{2-4,6-8}.

The aim of this report is to present a case of Olanzapine-induced diabetic ketoacidosis and review of the literature.

THE CASE

A twenty-seven-year-old Saudi woman with a 10-year history of bipolar affective disorder, requiring numerous hospitalizations; she had neither personal nor family history of diabetes mellitus (DM). Her medical history was notable for obesity, her prior psychopharmacological treatment included trials of neuroleptics (Perphenazine, Trifluoperazine, Haloperidol,

* Assistant Professor of Psychiatry
Department of Internal Medicine
College of Medicine
King Khalid University
Abha, Kingdom of Saudi Arabia
Email: hasanalamri@ymail.com

Risperidone), anticonvulsants (Valproic Acid, Carbamazepine), antidepressants (Fluoxetine, Paroxetine, Escitalopram), and anxiolytics (Clonazepam, Lorazepam).

After several months of non-compliance with her psychotropic regimen, she decompensated psychiatrically, and she was admitted to Mental Hospital on 31 January 2006 because of manic episode. On admission, Olanzapine (15 mg q.i.d.) and Clonazepam (2 mg bid) were initiated. Laboratory studies conducted before treatment with Olanzapine revealed normal random serum glucose levels. Her body weight was 75 kg, and her body mass index (BMI) was 33.3 kg/m². She spent seven days in the hospital; her psychiatric symptoms were controlled. On discharge, controlled-release sodium valproate (750 mg bid) was added to her regimen and Olanzapine dose was decreased to 10 mg/day. Two weeks later, she was seen in the clinic and she was psychologically stable.

On 13 April 2006, she was seen in the emergency department because of progressive somnolence, polyuria, and polydipsia. Serum chemistries revealed serum glucose of 800 mg/dL, and urine was positive (+3) for ketones. She was diagnosed as being in diabetic ketoacidosis (DKA) and was transferred to a general hospital for further management. She was admitted to the intermediate intensive care unit (IICU). On admission, her laboratory results were: sodium 135 mmol/L, potassium 4.5 mmol/L, chloride 103 mmol/L, calcium 9 mg/dL, blood pH 7.39, bicarbonate 20.3 mmol/L, urea 31 mg/dL, creatinine 1 mg/dL, and white cell count 3.4 x 10⁹ /L. Liver function tests (LFTs), triglycerides and cholesterol were within normal limits, and all other laboratory data were within normal limits. Her weight had increased 9 kg; therefore, she had a weight of 84 kg, for a body mass index of 37.3 kg/m².

During her hospital stay, the patient was treated with intravenous fluids and insulin. She was placed on a sliding scale insulin regimen besides Metformin (500 mg t.i.d.). Olanzapine was discontinued and replaced with Haloperidol 5 mg/day. Subsequently, glucose concentrations slowly decreased and ketosis resolved. No source of infection was found. The patient took part in diabetes and dietary education. She was discharged from hospital on day 7 on a subcutaneous (sc) insulin regimen of NPH (50 U q AM and 25 U q PM), and regular insulin (10 U q AM and 10 U q PM), Metformin (500 mg three times daily), controlled-release sodium valproate (500 mg bid), and Haloperidol (5 mg q.i.d.).

After discharge, the patient requirements for insulin have been slowly decreasing and she had no more hospitalizations or emergency department visits. The fasting glucose concentrations have been within the normal range. She has made minimal adjustments to her diet and exercise and has lost no weight. Bipolar disorder has been adequately controlled with controlled-release Sodium Valproate and Haloperidol. Despite having discontinued Olanzapine, she still requires insulin.

DISCUSSION

The present case corroborates and extends some recent case reports of new-onset DM and diabetic ketoacidosis associated with Olanzapine treatment³⁻¹¹. Our patient had been taking Olanzapine for approximately nine weeks when the episode occurred. Even after cessation of Olanzapine for six months, the patient still needs dietary restriction and insulin injections to

maintain normal blood glucose level. The question of whether diabetes mellitus will resolve after cessation of Olanzapine has not been conclusively answered^{7,12}.

Many patients required insulin therapy continuously, and in some, the diabetes reportedly was reversible after discontinuing the antipsychotic agent⁷. The length of time necessary for plasma glucose levels to return to normal after discontinuation of Olanzapine is also unclear. In addition, it is uncertain whether this adverse effect is dose dependent.

Although no conclusive evidence exists as to exactly how Olanzapine induces glucose dysregulation, several hypotheses have been put forth. Given the well-known potential for Olanzapine to cause weight gain, insulin resistance appears more likely to develop in patients who experience glucose dysregulation or weight gain¹³⁻¹⁴. However, in other case reports, glucose dysregulation occurred days or months after the start of Olanzapine and in the presence or absence of weight gain⁵. This suggests that other mechanisms may be involved.

Several authors have speculated on possible mechanisms by which atypical antipsychotic medications might decrease insulin output, including toxic effect on pancreatic islet cells, sympathetic nervous system dysregulation, or the physiologic effect of serotonin antagonism on the b cells⁷. Another postulated mechanism is that atypical antipsychotic agents may decrease the half-life or number of glucose transporters, thereby making fewer transporters available to carry glucose, which would increase the amount of glucose in the blood¹⁵. Concomitant therapy (e.g., Olanzapine with Valproic acid) could also lead to or exacerbate hyperglycemia. Indeed, Valproic acid itself has caused dramatic increases in weight as well as insulin resistance in women¹⁶. However, our patient had been taking Valproic acid for many years, and this medication has not been found to cause DKA. In the absence of epidemiologic or experimental data; however, these ideas are simply speculations and the underlying mechanism may be a combination of these factors.

The decision whether to stop or continue Olanzapine is difficult without systematic data on diabetogenic risk profiles of Olanzapine. In some patients, Olanzapine was the best antipsychotic to control their conditions and Olanzapine could be discontinued because of the risk of psychotic worsening. In this case, Olanzapine could be discontinued with minimal effective dose besides antidiabetic therapy. In addition, discontinuing the offending antipsychotic agent while a patient is receiving insulin could lead to hypoglycemia if the antipsychotic agent was precipitating the hyperglycemia. This could happen in non-compliant patients who stop taking their antipsychotic drugs. Awareness of these risks and issues will help clinicians and patients better benefit from the proven efficacy of Olanzapine.

This case illustrates the importance of being alert to the possibility of Olanzapine-induced diabetes mellitus. In Saudi Arabia, no guidelines for screening patients with fasting blood glucose levels before starting therapy with Olanzapine or any other antipsychotic agents. Until causality is proven, clinicians may consider obtaining baseline and periodic glucose measurements in patients with predisposing factors for diabetes mellitus or sustained weight gain. Given the risk of weight gain with Olanzapine, families should be educated about diet and exercise options that may help prevent or minimize this adverse effect. Olanzapine education about symptoms of diabetes and its complications is very important, polyuria and recent significant weight gain in patients taking Olanzapine may be early warning signs.

CONCLUSION

In this report, we have presented a twenty-seven-year-old Saudi woman with a 10-year history of bipolar affective disorder who required numerous hospitalizations and developed diabetic ketoacidosis after treatment with Olanzapine for few months.

REFERENCES

1. Janicak P, Davis J, Preskorn S, et al. Principles and Practice of Psychopharmacology, 2nd Edition. Baltimore, Lippincott Williams, & Wilkins; Fourth Edition, 2006.
2. Dyer O: Lilly Investigated in US Over the Marketing of Olanzapine. *BMJ* 2007; 334: 171.
3. Bettinger TL, Mendelson SC, Dorson PG, et al. Olanzapine-induced Glucose Dysregulation. *Ann Pharmacother* 2000; 34: 865-7.
4. Rigalleau V, Gatta B, Bonnaud M, et al. Diabetes as a Result of Atypical Anti-psychotic Drugs: A Report of Three Cases. *Diabet Med* 2000; 17: 484-6.
5. Paizis M, Cavaleri S, Schwarz ME, et al. Acute-onset Diabetic Ketoacidosis During Olanzapine Treatment in a Patient without Pretreatment Obesity or Treatment-associated Weight Gain. *Primary Psychiatry* 1999; 37-8.
6. Wirshing DA, Spellberg GJ, Erhart SM, et al. Novel Antipsychotics and New-onset Diabetes. *Biol Psychiatry* 1998; 44: 778-83.
7. Goldstein LE, Sporn J, Brown S, et al. New-onset Diabetes Mellitus and Diabetic Ketoacidosis Associated with Olanzapine Treatment. *Psychosomatics* 1999; 40: 438-43.
8. Wong JO, Fu JC, Hung GB. Olanzapine-induced Diabetic Ketoacidosis in a Chinese man. *Hong Kong Med J* 2007; 13: 73-4.
9. Sernyak MJ, Leslie DL, Alarcon RD, et al. Association of Diabetes Mellitus with Use of Atypical Neuroleptics in the Treatment of Schizophrenia. *Am J Psychiatry* 2002; 159: 561-6.
10. Gianfrancesco FD, Grogg AL, Mahmoud RA, et al. 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: 920-30.
11. Leslie DL, Rosenheck RA. Incidence of Newly Diagnosed Diabetes Attributable to Atypical Antipsychotic Medications. *Am J Psychiatry* 2004; 161: 1709-11.
12. Straker D, Mendelowitz A, Karlin L. Near Fatal Ketoacidosis with Olanzapine Treatment. *Psychosomatics* 2002; 43: 339-40.
13. Kraus T, Haack M, Schuld A, et al. Body Weight and Leptin Plasma Levels During Treatment with Antipsychotic Drugs. *Am J Psychiatry* 1999; 156: 312-4.
14. Gupta S, Droney T, Al-Samarrai S, et al. Olanzapine-induced Weight Gain. *Ann Clin Psychiatry* 1998; 10 (1): 39.
15. Goldstein LE, Henderson DC. Atypical Antipsychotic Agents and Diabetes Mellitus. *Primary Psych* 2000; 7(5): 65-8.
16. Isojarvi JT, Laatikainen TJ, Knip M. Obesity and Endocrine Disorders in Women Taking Valproate for Epilepsy. *Ann Neurol* 1996; 39: 579-84.