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Case Report

Olanzapine-Induced Diabetic Ketoacidosis: A Reversible Etiology Overlooked in Psychiatric Patients

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ABSTRACT

Background/Objective: Olanzapine is a second-generation antipsychotic medication with increased side effects of weight gain, hyperglycemia, and insulin resistance. Here we describe a case of diabetic ketoacidosis in a patient who started taking olanzapine 12 weeks before she presented.
Case Report: A 73-year-old African-American female presented with a 1-week history of confusion, polyuria, and polydipsia. Her past medical history included type 2 diabetes mellitus, hyperlipidemia, and severe depression with psychotic features. Her medications were olanzapine 5 mg, duloxetine 90 mg, and rosuvastatin 5 mg daily. Three weeks prior, she was diagnosed with COVID-19 and treated for a urinary tract infection. Her physical exam upon admission included severely dry mucous membranes and labored respirations. The circulating glucose was 748 mg/dL (70-110), anion gap 39 mmol/L (7-16), and hemoglobin A1c (HgbA1c) 11.8% (105 mmol/mol). Three months prior, her HgbA1c was 6.7% (50 mmol/mol). She was treated with intravenous fluids and continuous insulin infusion followed by subcutaneous basal-bolus glargine and lispro after an anion gap of 13 mmol/L (7-16) was obtained. Two weeks into her hospitalization, olanzapine was discontinued. She was discharged on 10 units of glargine and metformin 500 mg twice daily. Five months after discharge, she indicated not taking any of the prescribed insulin or metformin. At this follow-up, her HgbA1c was 6.7%.
Discussion: Olanzapine may impair insulin secretion by causing pancreatic beta-cell apoptosis.
Conclusion: Increased awareness of the generalized metabolic effects and risk of diabetic ketoacidosis associated with antipsychotic medications is needed to develop a safe treatment plan for patients.

Introduction

Olanzapine is a second-generation antipsychotic medication that has a relatively low risk of inducing extrapyramidal side effects. Chronic treatment with olanzapine has been associated with weight gain, hyperglycemia, and insulin resistance, inducing or aggravating diabetes mellitus and metabolic syndrome.[1] Although a rare complication, diabetic ketoacidosis (DKA) can result. Here we present a case of diabetes ketoacidosis that developed after the patient was started on olanzapine.

Case Report

A 73-year-old female presented with 1-week onset of confusion, polyuria, and polydipsia. Her past medical history included type 2 diabetes without microvascular or macrovascular complications, hyperlipidemia, and severe depression with psychotic features. Three weeks prior to her presentation, she was diagnosed with COVID-19 infection but did not require supplemental oxygen, glucocorticoid therapy, or hospitalization. She also had a urinary tract infection (UTI) treated with a course of sulfamethoxazole-trimethoprim (800 mg-160 mg). Her medications were olanzapine 5 mg, duloxetine 90 mg, and rosuvastatin 5 mg daily. Her blood pressure was 156/95 mmHg, heart rate was 107 beats per minute,

Abbreviations: DKA, diabetic ketoacidosis; ECT, electroconvulsive therapy; HgbA1c, hemoglobin A1c; UTI, urinary tract infection.

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respiratory rate was 31 breaths per minute, and blood oxygen saturation was 96%. Her mucous membranes upon admission were severely dry, and respirations were labored. There were no focal neurologic deficits or focal areas of abdominal tenderness. Her urinalysis was positive for ketones and glucose. As shown in Table, the serum glucose was 748 mg/dL (70-110), creatinine 2.14 mg/dL (0.6-1.2), potassium 5.4 mg/dL (3.5-5.0), anion gap 39 mmol/L (7-16), bicarbonate 10 mmol/L (23-30), pH 7.14 (7.32-7.42), beta-hydroxybutyrate 9.18 mmol/L (<0.4), and hemoglobin A1c (HgbA1c) of 11.8% (<5.7%). The antiglutamic acid decarboxylase antibody was negative. Three months previously, her HgbA1c was 6.7% (<5.7%).

She received intravenous fluid resuscitation with 0.9% normal saline and a continuous insulin infusion. Consecutive lab checks showed an anion gap of 13 mmol/L (7-16). Her continuous insulin was bridged with 10 units of subcutaneous Neutral Protamine Hagedorn insulin. Two hours later, the continuous infusion was discontinued and a subcutaneous basal-bolus insulin regimen of 10 units of glargine and 7 units of lispro three times a day before meals (AC) was started. On day 2, the patient received 14 units of glargine and was on continuous 0.45% saline at 175 cc/h. On day 3, the patient's anion gap was noted to be 20 and continuous insulin was reinitiated. By day 5, her anion gap was 11 mmol/L (7-16), and she was transitioned to a subcutaneous basal-bolus regimen of 27 units of glargine and 8 units of lispro three times a day AC with a 2-hour overlap.

The patient remained in the hospital for 7 days while waiting for psychiatric consultation and electroconvulsive therapy (ECT). During this time, her regimen was decreased to 18 units of glargine and 7 units of lispro three times a day AC because her blood sugars were within acceptable hospital range of 140 mg/dL (7.8 mmol/L) and 180 mg/dL (10.0 mmol/L). On day 12, the patient was made Nil Per Os (nothing by mouth) for her ECT procedure. After receiving ECT, a diet was not restarted, and the patient overnight had a hypoglycemic episode with a point-of-care glucose of 58 mg/dL. She was asymptomatic and received oral dextrose gel. Repeat point of care in the morning was 89 mg/dL. Her regimen was decreased to 10 units of glargine and 7 units of lispro three times a day AC.

On day 14, one of her daily medications, olanzapine was discontinued. She was discharged with 10 units of glargine nightly and metformin 500 mg twice daily. She was also advised by the psychiatry team to switch from olanzapine to risperidone. Five months later at follow-up, the patient's primary caregivers reported not administering any of the prescribed medications to the patient. Her repeat HgbA1c was 6.7% (50 mmol/L).

Discussion

Herein we present a 73-year-old African-American female with a more than 10-year-history of type 2 diabetes mellitus without microvascular or macrovascular complications. She was started on a new antipsychotic regimen, and 3 months later, she presented to the hospital for the first time with DKA. Clinical presentation of DKA is oftentimes the very first sign of antipsychotic-induced diabetes mellitus.[2] Prevalence of diabetes mellitus presenting as DKA is 10 times higher in those using antipsychotics than the general population presenting with simply classic symptoms of polyuria and polydipsia.[2] The prevalence of this occurring is 30 times higher in those with pre-existing diabetes.[2]

Patient risk factors identified in prior medical literature include those of non-Caucasian ethnicity with type 1 diabetes, prediabetes, and/or with acute physical illness.[3,4] There is also a genetic predisposition for the African-American race.[4] The patient did receive multiple rounds of ECT in those 3 months, but there is limited and conflicting literature regarding the effects of individual ECT treatments on blood glucose.[5] Also, taking day 3 of her clinical presentation into consideration, she may have reverted to DKA again due to insufficient longer-acting insulin.

Infection is the most common precipitating factor for DKA.[6] This patient did have both a UTI and nonhypoxic COVID-19 infection about 3 weeks prior to presentation. Different theories exist regarding the influence SARS-CoV-2 virus has on patients with diabetes mellitus. The proinflammatory cytokine storm and a decreased angiotensin-converting enzyme 2 enzyme expression on pancreatic islet cells can lead to local inflammation, apoptosis, and hyperglycemia.[7] A study including 658 hospitalized patients with COVID-19 showed 42 of them had developed ketosis and 5 developed DKA, 2 of which were not previously diagnosed with diabetes

Highlights

- Olanzapine can contribute to the etiology of diabetic ketoacidosis.
- Discontinuing olanzapine can lead to improvements in hyperglycemia and hemoglobin A1c.
- Those with prediabetes or diabetes mellitus on olanzapine need extra precautions.

Clinical Relevance

Diabetic ketoacidosis resulting from long-term use of atypical antipsychotics is a rare complication. There are only 85 reported cases over the last 25 years. This serves to educate physicians about the significant side effect profile of olanzapine and stresses the need for specific practice guidelines for patients with diabetes on antipsychotics.

Table
Initial Laboratory Measurements Upon Hospital Admission

Test	Value	Reference range
Serum glucose	748	70-110 mg/dL
Creatinine	2.14	0.60-1.20 mg/dL
Potassium	5.4	3.5-5.0 mmol/L
Bicarbonate	10	23-30 mmol/L
Anion gap	39	7-16 mmol/L
pH mixed venous	7.14	7.32-7.42
Beta-hydroxybutyrate	9.18	<0.4 mmol/L
Hemoglobin A1c	11.8% (105)	<5.7% (<39 mmol/mol)
C-peptide	0.49	0.80-3.85 ng/mL
Antiglutamic acid decarboxylase antibody	<5	<5 [IU]/mL
Urinalysis: ketones	2+	Negative
Urinalysis: glucose	4+	Negative

mellitus.[7] More data are required to understand how this virus can cause ketoacidosis, and literature has only examined patients with COVID-19 infection active at the time of their admission. The patient discussed here was COVID-19-negative upon admission, and her prior infection did not require any monoclonal antibodies, glucocorticoids, or oxygen therapy. Her concomitant UTI before admission was actively treated with oral antibiotics outpatient and did not result in any severe complications like emphysematous or gangrenous cystitis.

The patient's differential diagnosis also included ketosis-prone type 2 diabetes mellitus. This subtype of diabetes is predominant in African-American and Hispanic patients, those who are obese, have a strong family history of diabetes, have low autoimmune markers, and lack human leukocyte antigen genetic association.[8,9] While this patient is African-American and has negative autoantibodies, she has a healthy body mass index of 23 kg/m^2 (18.5-24.9), and it is unknown if she has a family history of diabetes. Limitations here include the patient not obtaining a follow-up C-peptide level. However, with her glucose levels within range (120-180 mg/dL) and significant improvement in her HgbA1c, it can be understood that she has some degree of preserved beta-cell function.

Besides the addition of olanzapine in those 3 months, this patient had no other lifestyle changes or inciting events that would have contributed to her uncontrolled glucose levels. What is novel here is that complete antipsychotic medication discontinuation and the lack of antihyperglycemic therapy allowed the patient to have significant improvement in her HgbA1c. Olanzapine can be identified as a reversible trigger for the patient's symptoms and a precipitating factor for her DKA.

There have been proposed mechanisms of how olanzapine can lead to hyperglycemia, hyperphagia, weight gain, and overall glucose intolerance. This includes hepatic glucose production through the activation of hypothalamic adenosine 5'-monophsphate-activated protein kinase, which antagonizes serotonin 5HT2C, histamine H1, dopamine D2, and alpha-1 adrenergic receptors.[1,10] Olanzapine can directly influence pancreatic beta-cells via apoptosis and/or impairing insulin secretion at an early stage of treatment.[11] It can cause stress on the endoplasmic reticulum in beta-cells, as seen by activation of stress sensor PKR-like endoplasmic reticulum kinase.[11,12] This thought was further supported by an undetectable phosphorylation of the alpha subunit of eukaryotic initiation factor 2, an event usually seen downstream of PKR-like endoplasmic reticulum kinase activation.[11,12]

There are long-standing management guidelines for DKA in practice today. This consists of intravenous and eventual subcutaneous insulin therapy with parallel glucose administration when blood glucose levels are less than 250 mg/dL, sufficient fluid resuscitation and electrolyte replacement, and treatment of underlying stressors or infections.[3,4,13] Specific guidelines should exist specifically for patients on antipsychotics, given the longevity of psychiatric treatment and high mortality rates of antipsychotic-associated DKA.[13]

Prior to initiation of olanzapine, psychiatrists should refer patients to primary care physicians or endocrinologists to screen for and enact preventative measures for diabetes, including initial physical and laboratory measurements such as fasting plasma glucose, body mass index, HgbA1c, and lipid profile.[3.5] Patients and caregivers should be educated on signs and symptoms of diabetes, and glycemia should be evaluated immediately if patients exhibit symptoms of polyuria or polydipsia while on olanzapine.[13]

This case highlights that severe olanzapine-induced hyperglycemia can be fully reversed with olanzapine discontinuation.[14] Patients should be closely monitored through a multidisciplinary lens. If antibodies are negative, physicians can slowly reduce and eventually omit insulin based on glycemic levels and introduce metformin therapy until HgbA1c is less than 6% to reduce insulin resistance.[3,4,13] Other antipsychotic agents can be considered to control psychiatric symptoms because not all have the same propensity to cause DKA.[4,15]

Conclusion

Proper guidelines must be established for regular monitoring of blood glucose levels before initiation and maintenance of treatment with olanzapine since it is now used as first-line treatment for psychosis and many other mood disorders. Extra precautions and education must be provided for those with pre-existing prediabetes or diabetes mellitus to avoid the risk of developing DKA. Increased awareness of the metabolic effects associated with antipsychotics is needed for psychiatrists and endocrinologists to work together and develop a safe treatment plan. Patient-specific risk factors must be taken into consideration when choosing an antipsychotic regimen.

Disclosure

The authors have no multiplicity of interest to disclose.

References

1. Ikegami M, Ikeda H, Ohashi T, Kai M, Osada M, Kamei A, Kamei J. Olanzapine-induced hyperglycemia: possible involvement of histaminergic, dopaminergic and adrenergic functions in the central nervous system. *Neuroendocrinology*. 2013;98(3):224–232.
2. Henderson DC, Cagliero E, Copeland PM, et al. Elevated hemoglobin A_{1c} as a possible indicator of diabetes mellitus and diabetic ketoacidosis in schizophrenia patients receiving atypical antipsychotics. *J Clin Psychiatry*. 2007;68:533–541.
3. Vuk A, Kuzman MR, Baretic M, Osvatic MM. Diabetic ketoacidosis associated with antipsychotic drugs: case reports and a review of literature. *Psychiatr Danub*. 2017;29(2):121–135.
4. Adhoni MZU, Assadi RR, Abbas S. One-year course of olanzapine-induced diabetic ketoacidosis: a case report. *Dubai Diabetes Endocrinol J*. 2021;27:158–161.
5. Rasmussen KG, Ryan DA, Mueller PS. Blood glucose before and after ECT treatments in Type 2 diabetic patients. *J ECT*. 2006;22(2):124–126.
6. Eledrisi MS, Elzouki AN. Management of diabetic ketoacidosis in adults: a narrative review. *Saudi J Med Med Sci*. 2020;8(3):165–173.
7. de Sá-Ferreira CO, da Costa CHM, Guimarães JCW, et al. Diabetic ketoacidosis and COVID-19: what have we learned so far? *Am J Physiol Endocrinol Metab*. 2022;322(1):E44–E53.
8. Guillermo E. Umpierrez; ketosis-prone type 2 diabetes: time to revise the classification of diabetes. *Diabetes Care*. 2006;29(12):2755–2757.
9. Smolenski S, George NM. Management of ketosis-prone type 2 diabetes mellitus. *J Am Assoc Nurse Pract*. 2019;31(7):430–436.
10. Munaza A, Shruti MG, Eric N. Atypical antipsychotics and metabolic complications. *Diabetes*. 2018;67(Supplement_1):714.
11. Nagamine T. Olanzapine and diabetic ketoacidosis: what is the underlying mechanism? *Innov Clin Neurosci*. 2018;15(3-4):11.
12. Ozasa R, Okada T, Nadanaka S, et al. The antipsychotic olanzapine induces apoptosis in insulin-secreting pancreatic B cells by blocking PERK-mediated translational attenuation. *Cell Struct Funct*. 2013;38(2):183–195.
13. Vuk A, Baretic M, Osvatic MM, Filipcic I, Jovanovic N, Kuzman MR. Treatment of diabetic ketoacidosis associated with antipsychotic medication: literature review. *J Clin Psychopharmacol*. 2017;37(5):584–589.
14. Kumar PN, Thomas B. Hyperglycemia associated with olanzapine treatment. *Indian J Psychiatry*. 2011;53(2):176–177.
15. Ramaswamy K, Kozma CM, Nasrallah H. Risk of diabetic ketoacidosis after exposure to risperidone or olanzapine. *Drug Saf*. 2007;30:589–599.