CASE REPORT

Olanzapine-Induced Diabetic Ketoacidosis Resulting in Prolongation of Hospital Stay: Clinical Outcome and Cost Issues

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INTRODUCTION

Atypical antipsychotics are as effective as traditional antipsychotics in the treatment of chronic psychotic disorders and are associated with fewer extrapyramidal symptoms.[1] Despite their lower propensity to induce extrapyramidal symptoms, these drugs are associated with other adverse effects, including anticholinergic effects, hypotension, sedation, sexual dysfunction, and weight gain.[2] Endocrine disturbances such as hyperglycemia, new-onset type 2 diabetes mellitus, and ketoacidosis have been associated with atypical antipsychotics, including olanzapine.[3]

Diabetic ketoacidosis is a serious, potentially life-threatening metabolic complication of diabetes mellitus.[4] Numerous cases of this adverse effect have been reported during treatment with clozapine and olanzapine, but fewer case reports have been published for risperidone and quetiapine.[3] We report a case of prolonged hospital stay resulting from olanzapine-induced diabetic ketoacidosis in a patient with no previous personal or family history of diabetes. This case illustrates the substantial morbidity associated with this adverse effect.

CASE REPORT

A patient of African Canadian descent was brought to the emergency department by ambulance after being found unresponsive at home.* The patient lived alone, and limited history was available initially. On presentation, the pulse was 120 beats per minute, and blood pressure was 90/60 mm Hg.

Initial laboratory results revealed markedly elevated serum glucose (44.8 µmol/L; normal range 5.0 to 11.0 µmol/L), serum osmolality (382 mosmol/L; normal range 275 to 295 mosmol/L), and anion gap (28 mmol/L; normal range 3 to 13 mmol/L). Blood gas analysis showed profound metabolic acidosis, with pH 7.16 (normal range 7.35 to 7.45), bicarbonate 5 mmol/L (normal range 21 to 28 mmol/L), and arterial pressure of carbon dioxide 16 mm Hg (normal range 35 to 45 mm Hg). Testing of both serum and urine yielded positive results for ketones. Glycosylated hemoglobin was 14.9% (normal range 4.5% to 6.5%).

The patient's medical history was significant for depression, anxiety disorder, one episode of psychosis necessitating admission to hospital, and hypertension. There was no prior personal or family history of diabetes mellitus. The patient was vague in providing the history, but reported symptoms of hyperglycemia, including polyuria and polydipsia, in the days leading up to admission. The patient denied symptoms of hyperglycemia in the previous months. The patient was obese (body mass index 31 kg/m^2) with no documented weight changes in the previous year.

Home medications included paroxetine 20 mg once daily, clonazepam 0.5 mg at bedtime, atenolol 75 mg once daily, hydrochlorothiazide 25 mg once daily, and olanzapine 10 mg once daily. Olanzapine had been initiated at 5 mg daily during a psychiatry admission for an episode of psychosis 18 months earlier and had been increased (by the family physician) to 10 mg daily 8 months before the current admission. The patient reported no weight gain after initiation of olanzapine. At the time of the admission, the patient had been taking

*Patient demographic information that was not deemed pertinent to the understanding of this case has been omitted to ensure patient confidentiality.

paroxetine for approximately 2 years, and atenolol and hydrochlorothiazide for an estimated 5 years. Fasting plasma glucose had been normal when tested by the patient's family physician 8 months before the current admission.

Early management in the emergency department consisted of intravenous fluid resuscitation, insulin infusion, and discontinuation of olanzapine. During the first 48 hours after admission, more than 200 units of insulin per day was required to reverse the ketosis. Subsequently, subcutaneous insulin was started, with the patient continuing to receive more than 140 units/day during the first week. The patient's condition stabilized over the next several days, and on day 9, the insulin regimen was continued as follows: insulin 30/70 28 units before breakfast and 12 units before supper, and insulin lispro 16 units with lunch to maintain blood glucose between 5 and 10 mmol/L. At week 3 the patient's insulin requirements decreased to insulin 30/70 28 units in the morning and 12 units in the evening. Insulin requirements throughout the patient's hospital stay are shown in Figure 1.

Metformin was initiated on day 15 of the hospital stay; the insulin dose was gradually decreased and was discontinued on hospital day 33, when serum glucose values had declined to normal. By week 5, the patient was tolerating metformin 500 mg twice daily, with blood glucose ranging between 4.5 and 10 mmol/L. The patient was discharged on day 44 of the hospital stay, receiving metformin 500 mg 3 times daily; insulin therapy was no longer required. At the time of discharge, the patient was not receiving any antipsychotic medications, on the recommendation of the consultant psychiatry service.

This patient's hospital stay was prolonged for several reasons. First, it was difficult to stabilize the insulin therapy early during the hospital stay. The patient showed limited insight into the disease and was unable to self-manage insulin therapy, despite the education efforts of the medical team and diabetes educators. This process was complicated by the patient's history of mental illness and lack of family support. The hospital admission was further prolonged because of development of a urinary tract infection and influenza during a circulating influenza outbreak on the inpatient medical unit.

DISCUSSION

Diabetic ketoacidosis is an important and potentially life-threatening side effect of olanzapine and other

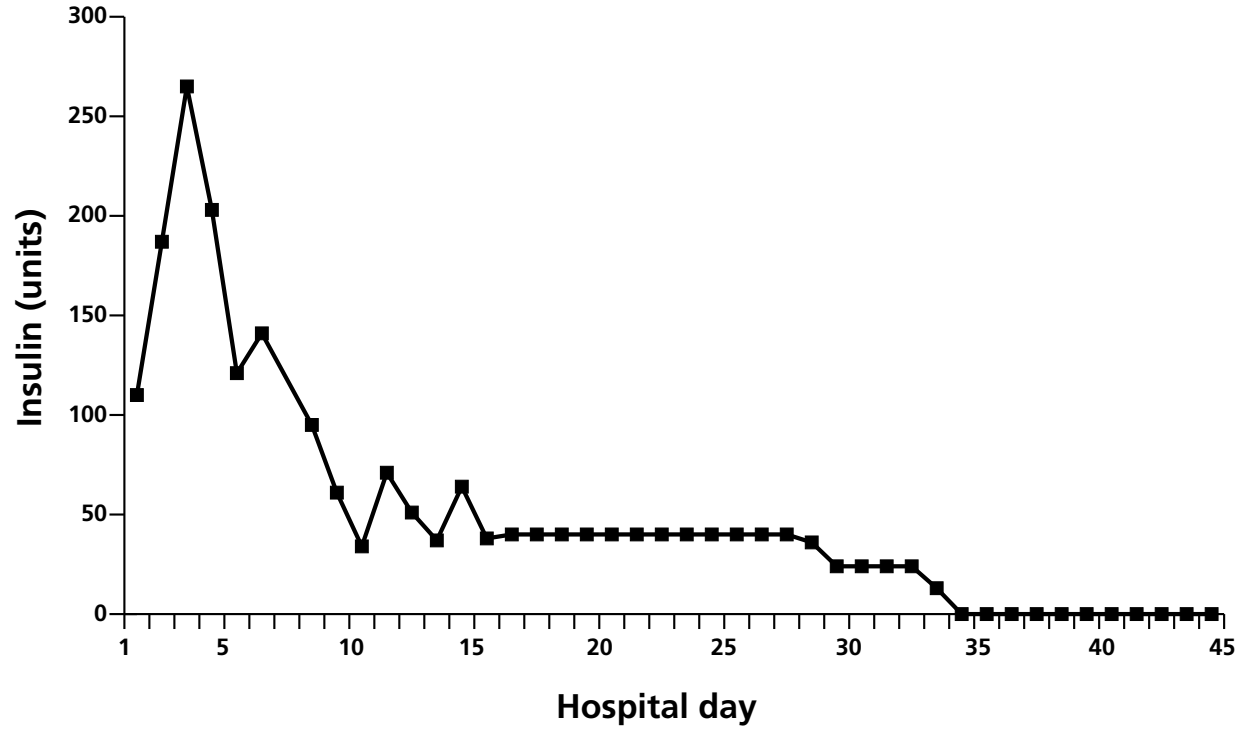

Figure 1. Daily insulin requirements during the hospital stay of a patient who presented with diabetic ketoacidosis associated with olanzapine therapy.

atypical antipsychotics. The true incidence of this adverse effect is not known. However, in one review, diabetic ketoacidosis was reported in 5 (4%) of 126 patients treated with atypical antipsychotics.[5] The mean time to onset in these 5 patients was 81 days (range 5 days to 40 weeks). In an analysis of 45 published cases of new-onset diabetes mellitus among patients receiving atypical antipsychotics, 19 (42%) of the patients initially presented with diabetic ketoacidosis.[6] The mean duration of atypical antipsychotic use before development of diabetes mellitus or diabetic ketoacidosis was 19 weeks (range 2–124 weeks).[6] The patient described here presented 18 months after initiation of olanzapine (8 months after an increase in the dose of this drug). This case highlights the need to monitor blood glucose throughout treatment with atypical antipsychotics and not simply in the period following initiation of the medication.

It has been postulated that, because of polymorphism, ketoacidosis is more likely to occur in genetically predisposed individuals.[7] The patient in this case was of African Canadian descent. African Americans have been disproportionately represented in case reports of diabetic ketoacidosis, which suggests that people with this ethnic background may be at greater risk. Jin and others[6] found that 47% of 45 published cases of new-onset diabetes mellitus or diabetic ketoacidosis with atypical antipsychotics involved African Americans. Clinicians should be aware of the apparently increased risk in this population and should adjust monitoring parameters and treatment choices accordingly.

The need for a prolonged hospital stay to manage this adverse drug reaction serves as a reminder of the costs of drug-induced and, in this case, preventable disease. In estimating the cost of drug therapy, the total costs should be considered, including those associated with treatment failure and adverse effects. In a recently published Veterans Affairs trial, olanzapine was equivalent in effect to haloperidol but was more expensive.[8] The costs for both outpatient day visits and inpatient care for issues other than mental health were greater (albeit not significantly so) for the patients receiving olanzapine, even when drug costs were excluded.

The cost of hospital management of diabetic ketoacidosis is substantial; in one US study, in which the average length of stay was 6.6 days, the cost was estimated at almost US$12,000 per patient.[9] Although costs calculated elsewhere cannot be directly applied to the patient described here, the cost in this case was substantial and probably even more than that estimated by Maldonado and others,[9] given the prolonged stay. In light of the other factors contributing to the prolonged hospital stay, it was not possible to calculate the costs directly associated with the olanzapine-induced diabetic ketoacidosis. However, based on a rather crude estimate of the daily cost of an acute care bed at our institution ($1200/day), the cost of this patient's 44-day stay can be estimated more than Can$50,000.

If 4% of patients receiving atypical antipsychotics experience diabetic ketoacidosis,[5] there is a need to more readily identify those at increased risk of such endocrine complications. When olanzapine or other atypical antipsychotics are used, it would seem prudent to monitor serum glucose levels regularly throughout therapy. Whether such a measure is useful in preventing diabetic ketoacidosis has yet to be determined.

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