Diabetic Ketoacidosis Possibly Precipitated by Loxapine

Marilyn J. Miller [1]

Abstract

This case describes the development of diabetic ketoacidosis in a middle-aged man with schizophrenia who had recently been prescribed loxapine. While there had been exposure to other antipsychotic medications, loxapine was the most recent addition to the regimen and a possible precipitant of the diabetic ketoacidosis. It is suggested that clinicians be alert to the possibility of new-onset diabetes in patients receiving both typical and atypical antipsychotics.

Key Words: Diabetes, Antipsychotic, Metabolic Side Effects

Introduction

Both typical and atypical antipsychotics have been associated with glucose abnormalities. By utilizing claims data, it was found that patients with schizophrenic illnesses who were users of antipsychotics, including both typicals and atypicals, experienced a 75% increase in risk of new-onset diabetes when compared to the general population (1) and, in patients receiving treatment for diabetes with oral hypoglycemics, deterioration of diabetic control and subsequent requirement for insulin has also been associated with antipsychotic use (2).

Among female patients hospitalized with a variety of psychotic illness, including schizophrenia, between 1955 and 1966, Thonnard-Newman (3) found the prevalence of diabetes rose from 4.2% of 450 patients to 17.2% of 528 patients after the introduction of chlorpromazine and other phenothiazine medications, with a 27% incidence of diabetes among those treated with phenothiazines. McKee, D'Arcy and Wilson (4) found that of 2,000 patients, 2.5% (forty-nine) were diabetic. Of those forty-nine patients, antipsychotic treatment had been initiated prior to the detection of diabetes in sixteen of the patients, and that fifteen of them had received high-dose chlorpromazine or another antipsychotic in equivalent doses from twelve months to many years prior to the diagnosis of diabetes. The researchers speculated that patients may have had a latent diabetic tendency, and that diabetes was precipitated by the antipsychotic drug treatment.

Loxapine has been associated with glucose abnormalities. Loxapine, a structural analog of clozapine, has been found to inhibit glucose uptake in neuronal cells in vitro (5) and was also among antipsychotic drugs found to induce hyperglycemia in mice (6). The following case describes a

[1] *Maryland VA Health Care System, Perry Point, MD*

Address for correspondence: Marilyn J. Miller, PhD, CRNP, CS-P, Nurse Practitioner/Clinical Specialist, Maryland VA Health Care System, Circle Drive, Perry Point, MD 21902
Phone: 410-642-2411, x5680; Fax: 410-642-1878;
E-mail: mil2wil2@comcast.net

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situation in which loxapine may have precipitated the development of diabetes mellitus. This case is of interest since not as much attention has been focused on monitoring glucose levels in patients receiving treatment with first-generation antipsychotics as compared to that of atypical antipsychotics.

Case

A fifty-six year old African-American male was reported, by his assisted living caretaker, to have been acting differently during the previous month. He had been sleeping during the day, and then was up all night. His mood was irritable. He believed that the food at his house was tainted, so he had been purchasing his own food.

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He was seen the same day in the mental health clinic and was found to be sleeping in the waiting room, but roused easily. His weight was 260 pounds, body mass index (BMI) 37, with a fifteen pound loss in one month. He complained of vomiting, lethargy and fatigue, an increase in thirst, and an increase in urination. Labs were drawn and revealed a glucose of 722 mg/dl and urinalysis with 3+ ketones. He was admitted to the hospital on acute medicine with a diagnosis of diabetic ketoacidosis (DKA) and new onset diabetes mellitus. His blood pressure (BP) was initially elevated to 146/87, but decreased to 129/67 the same day. A complete lipid panel was not available, but his total cholesterol was 372 mg/dl. There was no data for Hgb A1C at the time of admission, but one month after the onset of diabetes, the patient's Hgb A1C was 7.5%. Loxapine treatment was not discontinued. Insulin was initiated, and he was discharged in stable condition on NPH human insulin 35 units twice a day.

The patient had no history of diabetes or abnormality of glucose tolerance and no family history of diabetes. Glucose had been checked eleven months prior to the diagnosis of DKA with a result of 92 mg/dl. At that time the patient's weight was 287 pounds, BMI 41, BP 120/80, total cholesterol 189 mg/dl, LDL 116 mg/dl, HDL 29 mg/dl, and triglycerides 219 mg/dl. There was no data for Hgb A1C. The patient had a history of paranoid schizophrenia, hypertension, gastroesophageal reflux disease, diverticulosis and obesity. He was a smoker and suffered from a chronic cough. Medications at the time of DKA diagnosis included:

- EC aspirin 325 mg daily
- Lactulose syrup two tablespoons daily
- Lamotrigine 100 mg twice a day
- Loradatine 10 mg one daily
- Loxapine 50 mg two twice a day
- Nifedipine SR 30 mg one daily
- Omeprazole SR 20 mg daily
- Ziprasidone 80 mg twice a day

In addition to the current medications, the patient also had been treated with numerous antipsychotic/mood stabilizing medications in the past, including lithium carbonate, thioridazine, risperidone and olanzapine. The patient had been receiving treatment with olanzapine for five years and ziprasidone for four years. There had been a weight gain of 100 pounds during the first year of olanzapine treatment that was sustained. Over almost a two-year period of time, medications had been adjusted in an effort to decrease weight gain thought to be related to olanzapine. Olanzapine was decreased and ziprasidone increased, then lamotrigine added while continuing to decrease olanzapine, then olanzapine was stopped completely and loxapine added. At the time that olanzapine was discontinued the patient's weight was 291 pounds, BMI 42, BP 130/90. There was no data for glucose, lipids or Hgb A1C at that time. The patient had not been receiving olanzapine for five months prior to the diagnosis of DKA and had been receiving loxapine for three months.

Discussion

This case points out the complexities in trying to determine the contribution that antipsychotic medications might play in the development of diabetes mellitus. Increasing age and obesity put the patient at higher risk of developing diabetes. The patient had been exposed to several antipsychotic medications in the past and was currently on both ziprasidone and loxapine, but loxapine was the most recent addition to his medication regimen. It is possible that diabetes developed during treatment with olanzapine as glucose had not been closely monitored during that time frame. A case is described in which a patient with no history of diabetes mellitus was receiving treatment with olanzapine and presented similarly with ketoacidosis and weight loss (7). This possibility lends support to the need for more frequent glucose monitoring in the presence of antipsychotic treatment.

Further, while not reported frequently, a case of non-ketotic hyperglycemia related to loxapine use that resolved with cessation of loxapine and recurred when the patient was given amoxapine, a medication with a common metabolite, has been described by Tollefson and Lesar (8).

The patient was diagnosed with Type II diabetes mellitus. It is possible for a patient with Type II diabetes to experience diabetic ketoacidosis in response to a precipitating event, such as an infection or a chemical. In Type I diabetes there is ultimately little or no insulin secreted and insulin is required for survival, while in Type II diabetes, insulin is often not needed for survival, but may be needed for diabetic control due to insulin resistance (9).

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Conclusions

Due to the past history of other antipsychotic medications and the presence of diabetic risk factors, it is not possible to pinpoint the cause of diabetes in this patient; however, the possibility exists that it was precipitated by the initiation of loxapine. In this case, the change in the patient's sleep schedule may have mistakenly been attributed to a medication side effect or a symptom of his illness. Therefore, it is important to be alert to the potential for the development of diabetes in patients receiving antipsychotic medications and to monitor glucose regularly. The Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes (10) includes recommendations for glucose monitoring for patients receiving second-generation antipsychotics. The Conference recommendations are that fasting glucose be obtained at baseline, three months after the initiation of an antipsychotic, then annually, or more often, in those at high risk for diabetes. While these recommendations are for second-generation antipsychotics, consideration may be given to applying them in all patients receiving antipsychotic medications. Clinicians also should be aware of the classic signs and symptoms of diabetic ketoacidosis which may include polyuria, polydipsia, weight loss, abdominal pain, nausea and vomiting, dehydration, weakness, poor skin turgor, tachycardia, Kussmaul's respirations, acetone breath, and change in mental status (11).

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