Case Report

Clozapine-induced Insulin-resistant Hyperglycemia in a Diabetic Patient

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ABSTRACT

Clozapine is superior to all other antipsychotics in treatment-resistant schizophrenia. However, metabolic side effects are common while treating patients with clozapine. Administering clozapine in a patient who already is diabetic involves careful weighing of risks and benefits. Here, we report our experience of starting clozapine in a known diabetic patient. Clozapine was started in a patient with treatment-resistant psychosis in view of suicidal risk. Her diabetes mellitus was under good control with oral medications. After initiation of clozapine, blood sugars increased several fold within few days. Blood glucose continued to increase even with high doses of insulin and insulin infusion. Finally, blood sugars came under control only after discontinuation of clozapine. Precautionary measures while initiating clozapine in a diabetic patient are suggested – close monitoring of blood sugar during the initial few days and intensive intervention if blood sugar levels increase. Discontinuation of clozapine should also be kept in mind as a last resort.

Key words: *Clozapine, diabetes mellitus, hyperglycemia, insulin resistance*

INTRODUCTION

Clozapine is a second-generation antipsychotic with antagonist activity at numerous receptors, including dopamine (D_1, D_2, D_3, D_4, D_5), serotonin (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}), muscarinic (M_1, M_2, M_3, M_5), α_1- and α_2-adrenergic, and histamine (H_1) receptors. In addition, clozapine is an agonist at muscarinic (M_4) receptors. Clozapine has several advantages over other second-generation antipsychotic medications. It has superior efficacy in treating treatment-resistant psychotic symptoms. It is also useful in the reduction of suicidal behaviors, including suicide attempts, hospitalizations, or rescue interventions to prevent suicide as shown in international suicide prevention trial.[1] Apart from potentially fatal adverse drug reactions such as agranulocytosis, myocarditis, and seizures, clozapine is also associated with metabolic adverse effects.

Patients with schizophrenia often have features of metabolic syndrome even before the onset of treatment. Since atypical antipsychotics are initiated as the first-line treatment of schizophrenia in most patients, a large number of patients already are already overweight

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and have glucose dysregulation by the time clozapine is initiated. Consideration of risk–benefit ratio may dictate a clinician to start clozapine even in a patient who already has glucose dyscontrol.

We describe the effects of clozapine on blood sugar control when following its initiation in a well-controlled diabetic and discuss the possible mechanisms underlying this.

CASE REPORT

Mrs. C, a 53-year-old homemaker educated up to ninth standard from upper socioeconomic status presented to us with a 25-year history of a psychiatric illness characterized by delusion of infidelity and a related delusion of persecution toward her spouse. She did not have any hallucinations, irrelevant speech, or disorganized behavior. There were no negative symptoms or deterioration in personality. However, there was marked impairment in her marital life as she would not allow her spouse out of her sight for more than an hour. Quarrels, accusations, and physical fights with her spouse were daily events in her life, resulting in social isolation of the couple. Before presentation, she had made two suicide attempts, one with overdose of antipsychotic medications and the other by cutting her wrist, both after confronting her spouse about his "extramarital affairs." She also had medical problems namely hypertension and diabetes mellitus for 4 years and both were under control with oral medications.

In the preceding 24 years, the patient had received adequate trials of risperidone, quetiapine, aripiprazole, asenapine, and ziprasidone, which she had tolerated up to the maximum recommended doses. In view of persistence of psychotic symptoms and suicidal risk, a trial of clozapine was attempted by us under inpatient care. Before initiating clozapine, her fasting blood sugars were found to be between 100 and 200 mg/dl with oral medications and insulin. After initiating clozapine, blood sugars started increasing within 3–4 days. A gradual worsening of blood sugar control was noted every 2–3 days corresponding to dose increases of clozapine. By the time we reached a dose of 150 mg of clozapine, her blood sugars were >400 mg/dl [See Figure 1]. The patient was started on insulin infusion as the blood sugars could not be brought under control even with high doses of insulin thrice a day. Hence, it was decided to withdraw clozapine. Within 2 days of stopping clozapine, her blood sugar levels showed a declining trend. Over the next 5 days, blood sugars were well under control.

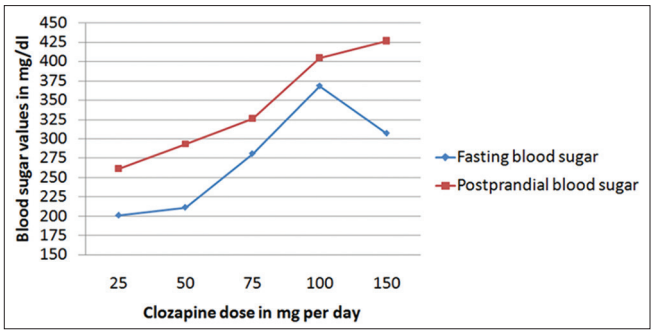

Figure 1: Relationship between clozapine dose and blood sugar values in our patient

DISCUSSION

Here, we present a case of marked worsening of hyperglycemia in a diabetic patient within few days of clozapine initiation. A score of six was obtained on Naranjo Nomogram which suggests that clozapine is the probable cause for this adverse effect. Gon *et al*.[2] reported a case of treatment-resistant schizophrenia and type 2 diabetes mellitus treated successfully with clozapine without worsening of blood sugar control. Hepburn and Brzozowska[3] reported a case of diabetic ketoacidosis and very severe hypertriglyceridemia which was associated with chronic clozapine use and successfully treated with continuous insulin infusion. Koller *et al*.[4] identified 384 reports of hyperglycemia as adverse event occurring in clozapine-treated patients. Of these, 54 patients had exacerbation of preexisting disease. The mean (±standard deviation) age was 40 ± 12 years. The male:female ratio was 2:0. It was reported that 46 out of 384 patients had improved glycemic control after discontinuation or dose reduction of the drug. Thus, the evidence regarding worsening of preexisting diabetes mellitus with clozapine treatment is mixed. The diabetic patient's response to clozapine initiation may lie anywhere in the continuum from no worsening to ketoacidosis.

Under basal conditions, glucose entry into the cell is mediated by glucose transporter 1 (GLUT1). On insulin stimulation, glucose entry into the cells is markedly increased, mediated by GLUT4 which is the insulin-sensitive GLUT. When insulin resistance develops, there is a suboptimal biological response to insulin, and as a result, there is compensatory hyperinsulinemia. When the increased level of insulin is inadequate to overcome insulin resistance, diabetes mellitus ensues. It has been proposed that propensity to block pancreatic M_3 receptors may underlie the hyperglycemia induced by antipsychotic drugs.[5] Clozapine may cause sugar dyscontrol by reduction of insulin secretion by beta cells of the pancreas or increase in insulin resistance[6] or by alteration in a

variety of regulatory molecules such as glucagon[7] and obestatin.[8]

Implications for clinical practice

Caution should be exercised while initiating clozapine for a diabetic patient. Worsening of blood sugars may occur within the first few days of initiating treatment, and thus, careful monitoring is required before initiating clozapine and in the early stages of titration. Early and intensive intervention should be attempted to control the blood sugar, and if found, ineffective withdrawal of clozapine should be considered.

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Conflicts of interest

There are no conflicts of interest.

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