Clozapine and Associated Diabetes Mellitus

Anand P. Popli, M.D., P. Eric Konicki, M.D.,
George J. Jurjus, M.D., Matthew A. Fuller, Pharm.D.,
and George E. Jaskiw, M.D.

Background: Clozapine is an effective therapy for the treatment of refractory psychosis. Clozapine-associated adverse effects include sedation, weight gain, sialorrhea, palpitations, seizures, and hematologic changes such as agranulocytosis.

Method: We present a four-case series in which clozapine use was associated with either a de novo onset or severe exacerbation of preexisting diabetes mellitus.

Results: The change in glycemic control was not significantly related to weight gain. Three of the patients have been able to continue on clozapine therapy and have experienced a reduction in psychotic symptoms.

Conclusion: Patients with a family history of diabetes mellitus or with preexisting diabetes mellitus may need to have blood sugar monitored closely during initiation of clozapine treatment.

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Received May 31, 1996; accepted Nov. 18, 1996. From the Psychiatry Service, Cleveland Veterans Affairs Medical Center and the Department of Psychiatry, Case Western Reserve University School of Medicine, Cleveland, Ohio.

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Reprint requests to: Anand P. Popli, M.D., Porter-Starke Counseling Centers, 601 Wall Street, Valparaiso, IN 46383.

Clozapine demonstrates superior clinical efficacy in refractory psychosis compared with typical antipsychotic drugs.[1] Although it induces fewer extrapyramidal symptoms than typical antipsychotic drugs, its use has been limited by other side effects, such as sedation, hypotension, seizures, and hematologic abnormalities. Clozapine induces a greater degree of weight gain than most neuroleptics.[2,3] One report also suggests that clozapine may raise triglyceride levels.[4] In addition, there have been four separate case reports, suggesting an association between clozapine treatment and hyperglycemia.[5–8] We now present a series of four cases in which clozapine use was associated with either new onset of diabetes mellitus or severe exacerbation of preexisting diabetes mellitus.

CASE REPORTS

Case 1

Mr. A, a 32-year-old black man, had paranoid schizophrenia (treatment refractory to typical antipsychotic drugs[1]) and intermittent cocaine abuse but no prior history or laboratory evidence of diabetes mellitus or glucose intolerance. He was 11% over ideal weight.[9] The patient's father had developed type I diabetes mellitus at the age of 32; a brother developed type II diabetes mellitus at the age of 31.

Clozapine was added and titrated to 425 mg/day over 6 weeks, while risperidone 6 mg/day was reduced and discontinued. Clozapine-associated side effects of sialorrhea, palpitations, and incontinence were effectively treated with clonidine 0.2 mg/day, propranolol 5 mg/day, and ephedrine 25 mg/day, respectively, and the patient had an excellent antipsychotic response. Increased appetite and weight gain (8 lb [3.6 kg]) over a 5-week period were noted. Eight weeks after starting clozapine, he experienced a hypotensive episode, which responded to the use of antiembolic stockings and the tapering of clonidine and propranolol. Several days later, he was found to be obtunded, dehydrated, and hypotensive. His medication regimen at that time was clozapine 425 mg/day and ephedrine 25 mg/day. Immediate serum laboratory values were a serum glucose level of 930 mg/dL, a pH of 7.22, moderate serum ketones, a serum osmolality of 376 mOsm/kg, and a BUN level of 53 mg/dL. Serum sodium was 142 mEq/L and serum potassium 6.2 mEq/L. The patient was treated in the intensive care unit for diabetic ketoacidosis and stabilized on daily insulin and intravenous fluids. Clozapine was discontinued. Owing to increased agitation and paranoia and severe treatment resistance, clozapine was restarted and titrated to 450 mg/day over 10 days. During the titration of clozapine, his insulin requirements fluctuated considerably. Subsequently, his insulin requirements decreased, and he was switched to 2.5 mg/day of glyburide with fair control (104–143 mg/dL) over the next 4 months. Whenever he stopped clozapine owing to noncompliance, his blood sugar levels normalized, and hyperglycemia returned when, after informed consent, he restarted clozapine. He has been treatment resistant to trials of the newer atypical antipsychotics.

Case 2

Mr. B, a 44-year-old black man with a 21-year history of treatment-refractory schizoaffective disorder, had no previous personal or family history of diabetes mellitus. Medical history was significant for glaucoma, hypertension, and obesity (42% over ideal body weight for height and frame).[8] Fasting blood sugar levels on two separate occasions, while Mr. B was on a stable regimen of risperidone 6 mg/day, hydrochlorothiazide 25 mg/day, and lithium 1200 mg/day, were normal.

Clozapine was added and titrated to 450 mg/day over 8 weeks. Psychotic symptoms improved, and there was minimal weight gain (3 lb [1.4 kg]). Emergent sialorrhea was treated with 0.1 mg of clonidine. Five weeks after Mr. B was started on clozapine treatment, mild hyperglycemia (198 mg/dL) was noted. The latter increased despite compliance with dietary restriction interventions (glucose: 494 mg/dL; hemoglobin A_{1c} [HbA_{1c}]: 8.7%). Serum electrolyte levels were in the normal range. Due to treatment refractoriness, after informed consent a decision was made to continue clozapine and treat the hyperglycemia. Glyburide 2.5 mg/day was started, and risperidone was tapered, with continuation of poor glycemic control. Over the following months, Mr. B was stabilized on a regimen of clozapine 675 mg/day, glyburide 30 mg/day, and methylphenidate 15 mg/day (for treatment of sedation). At 6-month follow-up, the patient continued to have abnormal glucose indices (blood sugar: 187–257 mg/dL; HbA_{1c}: 8.2%).

Case 3

Mr. C, a 51-year-old white man, presented with treatment-refractory schizophrenia and a 1-year history of type II diabetes mellitus, well controlled (130–141 mg/dL) by glyburide 12.5 mg/day. Thioridazine 300 mg/day was tapered over 5 days in preparation for a double-blind, randomized study comparing clozapine and haloperidol.

Within 2 weeks of starting the study, he experienced drooling, sedation, and increased blood sugar levels (300–500 mg/dL). Glyburide was gradually increased from 12.5 mg/day to 30 mg/day with poor results. The patient experienced dehydration, and the study medication was discontinued. The BUN level was elevated (36 mg/dL), and serum sodium, potassium, and chloride levels were 128 mEq/L, 5 mEq/L, and 94 mEq/L, respectively. It was determined that he had been taking clozapine 200 mg/day for 20 days. The patient's medical condition improved after treatment with NPH insulin and intravenous antibiotics for possible pneumonia, but increasing psychotic symptoms did not respond to thioridazine. Due to treatment refractoriness with typical antipsychotic drugs, he consented to an open trial of clozapine 200 mg/day and showed a good response. Over the course of the next year, he was able to live in a group home, stabilized on a regimen of 200 mg/day of clozapine and up to 67 units of insulin/day with moderate control (blood sugar: 181–361 mg/dL; HbA_{1c}: 7.3%–9.8%). Throughout, his weight has remained stable.

Case 4

Mr. D, a 51-year-old black man, had treatment-refractory schizophrenia, hypertension controlled with lisinopril 30 mg/day, arthritis, and adult-onset diabetes mellitus well controlled by glyburide 20 mg/day.

He was randomly assigned to receive clozapine in a double-blind study and slowly titrated to the maximum permitted dose (for clozapine, 900 mg/day). There was no improvement in psychotic symptoms over a 4-month period. Glycemic control worsened (blood sugar levels: 139–311 mg/dL; HbA_{1c}: 6.4) and required the use of insulin 78 units/day. There was no change in his serum electrolyte levels. Due to poor antipsychotic response, he was withdrawn from the study, and the blind was broken. He was subsequently treated with a combination of risperidone 6 mg/day and chlorpromazine 600 mg/day and showed moderate improvement. After discontinuation of clozapine, blood sugar levels began to decrease. Insulin was replaced by glyburide 20 mg/day, which was then reduced to 10 mg/day. The patient remained stable over the course of the following year.

DISCUSSION

We report on four patients who developed increasing glucose intolerance after starting clozapine treatment. The strength of the association is mitigated by several considerations. Both Mr. A and Mr. B developed diabetes mellitus de novo during clozapine treatment. Mr. A had a strong family history and was withdrawn from clonidine and propranolol prior to the onset of severe diabetic ketoacidosis. We are unaware of ketoacidosis in response to the discontinuation of these drugs. Mr. B was treated with concomitant hydrochlorothiazide and lithium carbonate. Although both drugs may alter glucose indices,[10,11] we note that the patient had been stable on these medications for many years, without any laboratory evidence of hyperglycemia, prior to the start of clozapine treatment. The combination of clozapine with other medications implicated in drug-induced diabetes mellitus may have an additive effect. In practice, drugs other than diazoxide or high-dose steroids[10] rarely induce glucose abnormalities requiring the addition of insulin (Table 1).

The cases of Mr. C and Mr. D have fewer potential confounds. Both patients suffered an exacerbation of their preexisting, but well-controlled, diabetes mellitus within 2 weeks of initiation of double-blind clozapine treatment. Both required the replacement of their initial oral hypoglycemic agent by insulin. It is noteworthy that

Table 1. Agents Implicated in Drug-Induced Diabetes Mellitus

Mechanism	Agents
Destruction of β-cells	Streptozocin, alloxan
Inhibition of insulin secretion by a direct effect on β-cells	Diazoxide, thiazide diuretics, loop diuretics, calcium channel blockers, phenytoin, pentamidine, L-asparaginase, cyclosporin-A, somatostatin
Sympathetic stimulation/ blockade	α- and β-agonists, α- and β-antagonists, xanthines
Impair insulin action	Corticosteroids, oral contraceptives, anabolic-androgenic steroids, aspirin
Unknown mechanisms	Morphine, encainide, nalidixic acid, rifampin, isoniazid, antidepressants, phenothiazines, butyrophenones, lithium, clozapine

Mr. D was able to return to his original oral hypoglycemic agent after discontinuing clozapine.

Our experience is consistent with four other published case reports. Kamran et al.[5] noted the new onset of severe sustained hyperglycemia requiring insulin after the start of clozapine treatment in a 41-year-old black man; hyperglycemia resolved after clozapine was discontinued. Koval et al.[6] noted that a 34-year-old black woman with a family history of diabetes mellitus developed de novo diabetic ketoacidosis within 6 weeks of initiation of clozapine. After clozapine was discontinued, her blood glucose normalized, and she required no further treatment with insulin or oral hypoglycemics. Cotreatment with clozapine and lithium was implicated in the onset of diabetic ketoacidosis in a 46-year-old black man with a family history of diabetes mellitus who was also on verapamil treatment for essential hypertension.[7] Kostakoğlu et al.[8] recently reported on a 42-year-old male patient with a family history of type II diabetes mellitus who developed insulin-dependent hyperglycemia and diabetic ketoacidosis with clozapine monotherapy. After clozapine treatment was stopped, his hyperglycemia resolved, and he required no further hypoglycemic drug. Isolated instances of hyperglycemia have also been noted in the postmarketing monitoring of clozapine (Sandoz Pharmaceuticals. 1995. Data on file).

In our own clinic, since 1989, we have instituted clozapine treatment in 147 patients. Thus, in our limited experience, the incidence of clinically significant changes in glucose tolerance during clozapine treatment was about 2.7%. This crude incidence does take into account the duration of exposure to clozapine. The small number of patients precludes a formal analysis of race-based differences, but we note that three of the four patients in our report are black, as were the three patients in other reported cases.[5–7] In the report from Turkey,[8] the race was not mentioned. The prevalence of non-insulin-dependent diabetes mellitus is higher in blacks at all ages.[12] Whether race influences the risk of developing or exacerbating diabetes mellitus during clozapine treatment remains to be determined in larger studies. Of our current patients (N = 93), 26% are black, and 88% are male.

If, as appears likely, clozapine can cause glucose abnormalities, the underlying mechanism is not obvious. Although weight gain has been implicated in the onset of type II diabetes mellitus, and clozapine can be associated with significant weight gain,[3] two of our patients had no change in weight and the other two had marginal weight gains (3 lb and 8 lb). There have been cases of pancreatitis reported in association with clozapine treatment.[13,14] Conceivably, clozapine could exert some inhibitory (via α_2- adrenergic receptors) or toxic effect on pancreatic isle receptors.[11,13,14] Given the paucity of reported cases, however, neither the mechanism nor the overall incidence of clozapine-associated glucose intolerance can be determined at this time.

CONCLUSION

Clinicians should consider monitoring glucose levels in patients, especially those with preexisting diabetes mellitus or a family history of diabetes mellitus, who are being considered for clozapine treatment. Black patients in particular may be at higher risk. Occult diabetes mellitus should be suspected in any patient newly started on clozapine treatment who develops an alteration of consciousness, polyuria, or increased thirst. In clozapine-responsive patients who develop hyperglycemia, the combination of clozapine with hypoglycemic agents should be considered after informed consent.

Drug names: chlorpromazine (Thorazine and others), clonidine (Catapres), clozapine (Clozaril), diazoxide (Proglycem and others), encainide (EnKaid), ephedrine (Mudrane and others), glyburide (Diabeta, Micronase), haloperidol (Haldol and others), hydrochlorothiazide (Dyazide and others), isoniazid (Cotinazin and others), L-asparaginase (Crasnitin, Elspar), lisinopril (Prinivil and others), methylphenidate (Ritalin), morphine (Duramorph and others), nalidixic acid (NegGram), pentamidine (Nebupent and others), phenytoin (Dilantin and others), propranolol (Inderal and others), rifampin (Rifadin and others), risperidone (Risperdal), streptozocin (Zanosar), thioridazine (Mellaril and others), verapamil (Calan and others).

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