Undiagnosed Hyperglycemia in Clozapine-Treated Patients With Schizophrenia

Michael J. Sernyak, M.D.; Barbara Gulanski, M.D.;
Douglas L. Leslie, Ph.D.; and Robert Rosenheck, M.D.

Background: Clozapine has been demonstrated to be superior to typical neuroleptics in reducing refractory symptoms in patients with schizophrenia, but it has also been associated with hyperglycemia and diabetes mellitus. This study was designed to investigate the proportion of undiagnosed impaired fasting glucose and diabetes mellitus in patients prescribed clozapine at 8 Department of Veterans Affairs (VA) medical centers.

Method: All patients diagnosed by the VA in New England with ICD-9 schizophrenia from Oct. 1, 1999, to Sept. 30, 2000, who received a prescription for clozapine were identified, and an attempt was made to obtain a fasting plasma glucose (FPG) test. All patients were also characterized as to whether they were diagnosed as diabetic prior to the screening FPG. Patients not previously diagnosed as diabetic were divided into 2 groups: normal FPG (< 110 mg/dL) and elevated FPG (≥ 110 mg/dL). Clinical and sociodemographic characteristics of the 2 groups were compared using chi-square and t tests.

Results: Overall, 121 patients were not previously diagnosed as diabetic and received an FPG. Ninety-three (77%) had a normal FPG, and 28 (23%) had an elevated plasma glucose—including 17% with impaired fasting glucose and 6% with diabetes. Patients with hyperglycemia were significantly older ($p = .007$) and more commonly codiagnosed with bipolar disorder ($p = .04$).

Conclusion: Hyperglycemia was common in patients receiving clozapine who had not been previously diagnosed as diabetic. These patients should be considered a group at high risk to develop diabetes mellitus and deserve both close monitoring and early intervention at the first sign of the onset of either diabetes or impaired glucose tolerance.

(J Clin Psychiatry 2003;64:605–608)

Received March 8, 2002; accepted Oct. 8, 2002. From the Psychiatry (Drs. Sernyak, Leslie, and Rosenheck) and Medicine (Dr. Gulanski) Services, VA Connecticut Healthcare System, and Yale University School of Medicine (all authors), New Haven, Conn.

Supported by the Department of Veterans Affairs VISN 1 Mental Illness Research, Education, and Clinical Center, West Haven, Conn.

Dr. Sernyak is a member of the speakers bureau or advisory board for Janssen.

The authors thank the Drug Benefit Management System in Hines, Ill., for supplying the prescription drug information used in this report.

Screening for diabetes in patients receiving clozapine began as a quality of care initiative from the mental health line managers within VISN 1 along with the network mental health service line manager Ethan S. Rofman, M.D.

Corresponding author and reprints: Michael J. Sernyak, M.D., Psychiatry Service, 116A VA Connecticut Healthcare System, West Haven Campus, 950 Campbell Ave., West Haven, CT 06516 (e-mail: michael.sernyak@yale.edu).

The atypical neuroleptic clozapine has been demonstrated to be superior to standard antipsychotics in reducing the treatment-refractory symptoms of patients with schizophrenia while inducing fewer extrapyramidal side effects.[1–7] However, there have been several reports of hyperglycemia and diabetes mellitus (type 1 and type 2) associated with clozapine use,[8–15] and clozapine has been found to induce insulin resistance.[16]

In a recent examination[17] of approximately 38,000 patients with schizophrenia who were prescribed neuroleptics in the Department of Veterans Affairs (VA), patients prescribed clozapine were 25% more likely to be diagnosed with diabetes than those receiving typical neuroleptics, after controlling for potentially confounding factors. A formal research study conducted in northern Sweden[13] demonstrated that 22% of patients receiving clozapine had an abnormality of glucose metabolism compared with 10% of patients receiving depot neuroleptics.

Not only has an increased rate of diagnosed diabetes mellitus been observed in patients receiving clozapine, there is the high likelihood that even this rate is an underestimate of the total number of patients treated with clozapine who have diabetes. The American Diabetes Association (ADA) estimates that 50% of patients with type 2 diabetes are undiagnosed.[18] The current study was designed to determine the proportion of undiagnosed diabetes mellitus and impaired fasting glucose (IFG) in a group of patients with schizophrenia being prescribed clozapine at 8 VA medical centers in New England.

METHOD

Patients

This study builds on data obtained from a quality of care initiative pursued throughout VA medical centers in New England. Using VA workload databases, all patients diagnosed with schizophrenia during fiscal year 2000 (October 1, 1999, to September 30, 2000) were identified. A diagnosis of schizophrenia was operationally defined as having at least 2 outpatient encounters in a specialty mental health outpatient clinic with either a primary or secondary diagnosis of schizophrenia—corresponding to the Ninth Revision, International Classification of Diseases (ICD-9) codes 295.00–295.99.[19] The ICD-9 is a commonly used coding scheme that encompasses both psychiatric and medical disorders.

Data describing patient characteristics such as age, income, gender, race, and ethnicity; receipt of VA compensation or pension; comorbid medical and psychiatric diagnoses; and the number and type of clinic visits were also obtained from VA administrative databases.

For all patients identified as having a diagnosis of schizophrenia, records of all medications prescribed during fiscal year 2000 were obtained from the VA's Drug Benefit Management System. If during the last week in which a prescription was received one of those prescriptions was written for clozapine, the patient was identified as receiving clozapine at the medical center indicated on the prescription. All of the names of patients identified as receiving clozapine at any of the VA medical centers in the New England region (VISN 1)—Connecticut; Providence, R.I.; Bedford, Boston, Brockton, and Northampton, Mass.; White River Junction, N.H.; and Togus, Me.—were then distributed to the appropriate medical center. Each medical center then attempted to obtain a fasting plasma glucose (FPG) on each of the patients identified and actually receiving clozapine.

Each patient was instructed to have blood drawn for plasma glucose analysis as early in the day as possible before eating or drinking anything. However, for the purposes of this study, a test was considered to be fasting only if the treating clinician was in agreement. For each patient receiving clozapine, a summary sheet was filled out that recorded the patient's vital signs, weight and height, the date of the blood draw, whether the test was judged by the treating clinician to be fasting or random, and the glucose value. Following ADA guidelines,[20] all FPG ≥ 126 mg/dL were repeated, on average several weeks later, to confirm the diagnosis of diabetes.

All plasma glucose concentrations were measured at the various medical centers using the Olympus AU640 Chemistry Analyzer that employs the hexokinase G-6-PDH method to determine the amount of glucose present in the plasma; with this method, a coefficient of variance of < 2% is reported (Olympus Optical Co., Ltd., Tokyo, Japan).

Use of these administrative data for research purposes was approved by the VA Connecticut Institutional Review Board.

Analysis

All patients who (1) were currently receiving clozapine, (2) were not identified as diabetic prior to FPG screening, and (3) had an FPG result available were included in the analysis. These patients were divided into 2 groups: those with an FPG < 110 mg/dL and those with an FPG ≥ 110 mg/dL (109 mg/dL represents the upper limit of normal in this test).[20] The initial analysis consisted of t tests and chi-square tests comparing the 2 groups with respect to demographic and clinical variables. For a second analysis, the groups were divided into 3 subgroups: normal (FPG < 110 mg/dL), IFG (FPG = 110 mg/dL to < 126 mg/dL), and diabetic (FPG ≥ 126 mg/dL). The subgroups were compared with respect to the same demographic and clinical variables described previously using analyses of variance and chi-square tests.

RESULTS

Patients with a diagnosis of schizophrenia who received clozapine (N = 168) were identified within VISN 1. For 20 of these patients, an FPG was not successfully obtained, although 27 additional patients were identified as diabetic prior to the FPG screening. Of the 121 patients not previously diagnosed as diabetic for whom an FPG was obtained, 93 (77%) had normal fasting blood sugar results (< 110 mg/dL), and 28 (23%) had a fasting blood sugar ≥ 110 mg/dL—with 21 (17%) having a result between 110 and 126 mg/dL and 7 (6%) having a result ≥ 126 mg/dL. Of the 7 with a result ≥ 126 mg/dL, 6 had second FPG ≥ 126 mg/dL. All 6 of these patients appeared clinically to have type 2 diabetes.

When patients (N = 93) with a normal FPG value were compared with those (N = 28) with an FPG ≥ 110 mg/dL, those with elevated FPG values were significantly older (mean ± SD years = 51.21 ± 9.34 vs. 46.16 ± 8.30; $F = 7.53$, df = 1,119; $p = .007$) and were significantly more likely to have comorbid bipolar disorder (N = 7 [25%] vs. N = 9 [9.7%]; $\chi^2 = 4.40$, df = 1, $p = .04$). There were no other significant differences between the 2 groups (Table 1).

Lastly, when the patients not previously identified as diabetic were divided into 3 subgroups—normal (FPG < 110 mg/dL), IFG (FPG = 110 mg/dL to < 126 mg/dL), and diabetic (FPG ≥ 126 mg/dL)—those patients with IFG were observed to be significantly older than the diabetic group, whereas the diabetic group had a significantly ($p < .05$) greater body mass index than either the normal or IFG groups (Table 2).

Table 1. Comparison of Groups by Fasting Plasma Glucose (FPG) Result

	FPG < 110 mg/dL (N = 93)		FPG ≥ 110 mg/dL (N = 28)		Analysis		
Characteristic	N	%	N	%	χ^2/F	df	p
Comorbid diagnosis							
Any substance abuse	15	16.1	6	21.4	0.42	1	.52
Other psychoses	10	10.8	4	14.3	0.26	1	.61
Bipolar	9	9.7	7	25	4.40	1	.04
Major depression	14	15.1	4	14.3	0.01	1	.92
Dysthymia	10	10.8	6	21.4	2.14	1	.14
PTSD	7	7.5	4	14.3	1.19	1	.28
Other anxiety disorder	8	8.6	5	17.9	1.92	1	.17
Personality disorder	5	5.4	2	7.1	0.12	1	.73
Men	87	93.6	27	96.4	0.33	1	.57
African American	9	9.7	3	10.7	0.03	1	.87
Hispanic	1	1.1	0	0	0.30	1	.58
Married	6	6.5	4	14.3	1.74	1	.19
Divorced/separated	17	18.3	5	17.9	0.00	1	.96
	Mean	SD	Mean	SD			
Age, y	46.2	8.3	51.2	9.3	7.53	1,119	.007
BMI[a]	28.8	4.8	28.6	5.5	0.04	1,114	.84
Annual income	$19,142	$8917	$18,985	$13,051	0.01	1,119	.94
Most recent GAF score	36.55	14.77	36.83	14.86	0	1,67	.94
Visits previous year							
Psychiatry/substance abuse	120	147	155	225	0.96	1,117	.36
Primary care	4.1	4.6	4.8	6.2	0.39	1,117	.53
Outpatient medicine	3.6	4.3	4.3	4.6	0.58	1,117	.45

[a][weight (kg)]/[height (meters)]^2.
Abbreviations: BMI = body mass index, GAF = Global Assessment of Functioning scale, PTSD = posttraumatic stress disorder.

Table 2. Comparison of Groups on Age and Body Mass Index (BMI)

	FPG Result (mg/dL)			Analysis			
Comparator	A < 110 (N = 93)	B 110 ≤ FPG < 126 (N = 21)	C ≥ 126 (N = 7)	F	df	p Value	Paired Comparison
Age, y							
Mean	46.2	51.7	49.7	3.88	2,118	.023	B > A
(SD)	(8.3)	(10.0)	(7.3)				
BMI[a]							
Mean	28.8	27.3	33.1	3.29	2,113	.041	C > B, A
(SD)	(4.8)	(5.0)	(5.1)				

[a][weight (kg)]/[height (meters)]^2.
Abbreviation: FPG = fasting plasma glucose.

DISCUSSION

Nearly one quarter (23%) of all nondiabetic patients with schizophrenia treated with clozapine in 8 VA medical centers had hyperglycemia. Within the group of patients with hyperglycemia, 21% (6/28) had second FPG ≥ 126 mg/dL—representing 6% of the entire nondiabetic sample.

Patients with second FPG ≥ 126 mg/dL are defined by the ADA to be diabetic,[20] and the risks associated with this illness are well described.[21] However, recent data also suggest that the glucose intolerance associated with FPG results between 110 and 126 mg/dL is also associated with increased cardiovascular morbidity and mortality even without the onset of frank diabetes[22,23] and that the onset of frank diabetes can be prevented by lifestyle changes once the risk is identified.[24]

Several limitations to this study deserve mentioning. The reliability of patients' compliance with fasting prior to drawing the FPG is unclear. It is worth noting that physicians assessed whether patients had fasted, and 12% (20/168) of the patients judged to be nonfasting were excluded from further analysis. While some of the FPG results may have been from nonfasting patients, this screening measure favors sensitivity over specificity. It is also unclear whether the proportion of false report of fasting in patients with schizophrenia is any greater than in the general population. Follow-up fasting plasma glucose monitoring was confirmatory in 86% (6/7) of patients with an initial FPG ≥ 126 mg/dL.

No information was available about the other medications the patients were receiving. Many medications have been implicated in altering glucose metabolism—including β-blockers and thiazide diuretics,[25] along with common psychiatric medications such as valproic acid and tricyclic antidepressants.[26] While use of these medications may be at least a partial explanation of why patients in this study with a comorbid diagnosis of bipolar disorder were significantly more likely to have an abnormal FPG, it should be acknowledged that at least one study[27] has shown an increased prevalence of type 2 diabetes among patients with bipolar and schizoaffective disorder independent of psychotropic drug use.

It is important to remember that this study was not designed to reach any conclusion concerning the causes of diabetes or hyperglycemia or their overall incidence in patients receiving clozapine. Rather, we were interested in how often hyperglycemia or diabetes mellitus goes undiagnosed in this particular treatment population. Similarly, these data do not allow a comparison of proportions of occult hyperglycemia attributable to clozapine and to other atypical or typical neuroleptics.

Among all patients initially identified as receiving clozapine, 27 were identified as diabetic prior to screening. As a result of the screening process, 6 patients were iden-

tified as diabetic after second FPG ≥ 126 mg/dL, yielding a proportion of approximately 4.5 cases of known diabetics for each previously unknown diabetic. Although this rate is much lower than the 1:1 ratio reported in the general population, it is consistent with clozapine patients receiving more medical monitoring than the general population and still illustrates the value of screening programs.

In sum, among nondiabetic patients with schizophrenia treated with clozapine in this study, nearly one quarter had an elevated fasting blood sugar screening. Given this proportion of previously undiscovered diabetes, we suggest that patients receiving clozapine should be considered a group at high risk to develop diabetes mellitus and that they deserve both close monitoring and early intervention at the first sign of the onset of either diabetes or impaired glucose tolerance.

Drug names: clozapine (Clozaril and others), valproic acid (Depakene and others).

REFERENCES

1. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45:789–796
2. Meltzer HY, Burnett S, Bastani B, et al. Effects of six months of clozapine treatment on the quality of life of chronic schizophrenic patients. Hosp Community Psychiatry 1990;41:892–897
3. Pickar D, Owen RR, Litman RE, et al. Clinical and biological response to clozapine in patients with schizophrenia: crossover comparison with fluphenazine. Arch Gen Psychiatry 1992;49:345–353
4. Breier A, Buchanan RW, Irish D, et al. Clozapine treatment of outpatients with schizophrenia: outcome and long-term response patterns. Hosp Community Psychiatry 1993;44:1145–1149
5. Breier A, Buchanan RW, Kirkpatrick B, et al. Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. Am J Psychiatry 1994;151:20–26
6. Lieberman JA, Safferman AZ, Pollack S, et al. Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. Am J Psychiatry 1994;151:1744–1752
7. Rosenheck R, Cramer J, Xu W, et al, for the Department of Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. N Engl J Med 1997;337:809–815
8. Kamran A, Doraiswamy PM, Jane JL, et al. Severe hyperglycemia associated with high doses of clozapine [letter]. Am J Psychiatry 1994;151:1395
9. Koval MS, Rames LJ, Christie S. Diabetic ketoacidosis associated with clozapine treatment [letter]. Am J Psychiatry 1994;151:1520–1521
10. Peterson GA, Byrd SL. Diabetic ketoacidosis from clozapine and lithium cotreatment [letter]. Am J Psychiatry 1996;153:737–738
11. Kostakoglu AE, Yazici KM, Erbas T, et al. Ketoacidosis as a side-effect of clozapine: a case report. Acta Psychiatr Scand 1996;93:217–218
12. Popli AP, Konicki PE, Jurjus GJ, et al. Clozapine and associated diabetes mellitus. J Clin Psychiatry 1997;58:108–111
13. Hägg S, Joelsson L, Mjörndal T, et al. Prevalence of diabetes and impaired glucose tolerance in patients treated with clozapine compared with patients treated with conventional depot neuroleptic medications. J Clin Psychiatry 1998;59:294–299
14. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998;44:778–783
15. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. Am J Psychiatry 2000;157:975–981
16. Melkersson KI, Hulting A-L, Brismar KE. Different influences of classical antipsychotics and clozapine on glucose-insulin homeostasis in patients with schizophrenia or related psychoses. J Clin Psychiatry 1999;60:783–791
17. Sernyak MJ, Leslie DL, Alarcon RD, et al. Association of diabetes mellitus with the use of atypical neuroleptics in the treatment of schizophrenia. Am J Psychiatry 2002;159:561–566
18. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2002;25(suppl 1):S5–S20
19. World Health Organization. Mental Disorders: Glossary and Guide to Their Classification in Accordance With the Ninth Revision of the International Classification of Diseases. Geneva, Switzerland: World Health Organization; 1978
20. Screening for type 2 diabetes. Diabetes Care 1999;22(suppl 1):S20–S23
21. Foster DW. Diabetes mellitus. In: Fauci A, Braunwald E, Isselbacher K, et al, eds. Harrison's Principles of Internal Medicine. New York, NY: McGraw-Hill; 1998:2060–2080
22. Khaw KT, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European prospective investigation of cancer and nutrition (EPIC-Norfolk). BMJ 2001;322:15–18
23. Fisman EZ, Motro M, Tenenbaum A, et al. Impaired fasting glucose concentrations in nondiabetic patients with ischemic heart disease: a marker for a worse prognosis. Am Heart J 2001;141:485–490
24. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Finnish Diabetes Prevention Study G: prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343–1350
25. Luna B, Feinglos M. Drug-induced hyperglycemia. JAMA 2001;286:1945–1948
26. Haupt DW, Newcomer JW. Hyperglycemia and antipsychotic medications. J Clin Psychiatry 2001;62(suppl 27):15–26
27. Regenold W, Thapar R, Marano C, et al. Increased prevalence of type 2 diabetes mellitus among psychiatric inpatients with bipolar I affective and schizoaffective disorders independent of psychotropic drug use. J Affect Disord 2002;70:19–26