Prevalence of Diabetes and Impaired Glucose Tolerance in Patients Treated With Clozapine Compared With Patients Treated With Conventional Depot Neuroleptic Medications

Staffan Hägg, M.D.; Lars Joelsson, M.D.; Tom Mjörndal, M.D., Ph.D.; Olav Spigset, M.D., Ph.D.; Greta Oja, R.N.; and Rune Dahlqvist, M.D., Ph.D.

Background: Recent case reports suggest the association of the emergence of diabetes mellitus with clozapine treatment, although conventional neuroleptics have also been implicated. This study was conducted to determine if there is an increased risk of diabetes mellitus and/or impaired glucose tolerance (IGT) during clozapine treatment compared with treatment with conventional depot neuroleptics.

Method: In a district hospital in northern Sweden, blood glucose tests and, if necessary, an oral glucose tolerance test were used to assess the prevalence of diabetes mellitus or IGT in 63 patients treated with clozapine compared with 67 patients treated with conventional depot neuroleptics (haloperidol, zuclopenthixol, fluphenazine, perphenazine, or flupenthixol). Diabetes mellitus and impaired glucose tolerance were classified according to World Health Organization criteria.

Results: There were 3 dropouts in the clozapine group and 4 in the control group. Of subjects treated with clozapine, 12% (7/60) had type 2 diabetes mellitus, and 10% (6/60) had IGT. Of subjects treated with depot injections of neuroleptics, 6% (4/63) had type 2 diabetes mellitus and 3% (2/63) had IGT. None in either group had type 1 diabetes mellitus. Subjects in the clozapine group were significantly ($p < .001$) younger than subjects in the control group, whereas the 2 groups did not differ with respect to body weight, body mass index, or prevalence of diabetes mellitus in first-degree relatives.

Conclusion: Subjects treated with clozapine were more often classified as having type 2 diabetes mellitus or IGT compared with subjects in the control group. This difference did not, however, achieve statistical significance ($p = .06$).

(J Clin Psychiatry 1998;59:294–299)

Received June 3, 1997; accepted Oct. 27, 1997. From the Division of Clinical Pharmacology, Norrland University Hospital (Drs. Hägg, Mjörndal, Spigset, and Dahlqvist), Umeå, and the Department of Psychiatry, Gällivare Hospital (Dr. Joelsson and Ms. Oja), Gällivare, Sweden.

Supported by the Sandoz AB, Täby, Sweden, and the County Council of Norrbotten Luleå, Sweden.

The authors thank Gunnel Persbo for analytical assistance and Lennart Nyström for comments.

Reprint requests to: Staffan Hägg, M.D., Division of Clinical Pharmacology, Norrland University Hospital, S-901 85 Umeå, Sweden.

Clozapine treatment has proved to be effective in patients with refractory schizophrenia and in patients intolerant to conventional neuroleptics.[1] The risk of developing acute extrapyramidal symptoms or tardive dyskinesia seems to be very small with clozapine treatment as opposed to treatment with conventional neuroleptic agents.[2] A number of other side effects, such as agranulocytosis, seizures, sedation, and hypersalivation have, however, limited the use of the drug.[2] The most serious side effect is agranulocytosis, which occurs in about 1% of the patients.[3]

Recently, case reports describing the emergence of de novo onset of diabetes mellitus or worsening of previously well-controlled diabetes after the start of treatment with clozapine have been published.[4–8] However, it has been reported that conventional neuroleptics also may alter glucose-insulin homeostasis.[9–12] Chlorpromazine has been used to prevent hypoglycemia in patients with malignant insulinoma,[13,14] and hyperglycemia has been observed in laboratory animals after ingestion of chlorpromazine.[15–18] Moreover, it has been reported that chlorpromazine can induce hyperglycemia in healthy volunteers and in patients with latent diabetes,[19] and, in 1 case report, loxapine and amoxapine, which are chemically related to clozapine, were reported to cause hyperglycemia.[20] Schizophrenia, however, has also been associated with an increased risk for developing hyperglycemia or diabetes mellitus.[21–25]

A cluster of cases with type 2 diabetes mellitus was observed at the psychiatric clinic of Gällivare Hospital. The present study was performed to investigate if treatment with clozapine involves an increased risk of developing diabetes mellitus compared with treatment with conventional neuroleptics.

METHOD

Subjects

The psychiatric clinic at Gällivare Hospital serves a large but sparsely populated area in northern Sweden comprising about 65,000 inhabitants. The population in this area principally consists of people of Swedish origin. There are, however, also small populations of Lapps, people of Finnish origin, and people originating from non-

Scandinavian countries. Clozapine was introduced at the Department of Psychiatry in 1990. Between that time and September 1, 1995, 89 patients between 22 and 65 years old had been treated with clozapine. Clozapine medication had been discontinued in 25 patients, and 1 subject had moved from the area. The remaining 63 patients were included in the study. The psychiatric diagnoses in these cases had been set by a psychiatrist according to the International Classification of Diseases, 9th Revision (ICD-9).[26] Fifty-eight patients had schizophrenia, 2 had paranoid psychosis, 2 had cycloid psychosis, and 1 had schizoaffective psychosis. Twelve subjects had concomitant treatment with conventional neuroleptics, most often haloperidol (N = 6).

On September 1, 1995, 125 patients between 26 and 65 years of age were undergoing treatment with depot-injections of neuroleptics. Forty-six of these patients were living in remote areas covered by the psychiatric clinic and were excluded from the study for practical reasons. Of the remaining 79 patients, 12 did not want to participate in the study. Thus, 67 patients were finally included. According to ICD-9 criteria, 53 patients had schizophrenia, 4 had paranoid psychosis, 3 had bipolar affective psychosis, 2 had cycloid psychosis, 2 had personality disorder, 2 had affective psychosis, and 1 had schizoaffective psychosis. They were treated with the following depot neuroleptics: haloperidol (N = 23), zuclopenthixol (N = 22), fluphenazine (N = 10), perphenazine (N = 8), and flupenthixol (N = 4). Some of these patients had additional treatment with oral neuroleptic medications (N = 37), most often levomepromazine (N = 26).

The clozapine group included 2 pairs of siblings and 1 aunt/nephew pair. The control group included 1 mother/child pair and 1 uncle/niece pair. One sibling pair was split: 1 sibling belonged to the clozapine group and the other to the control group.

The study was approved by the regional Ethics Committee at Umeå University Hospital. Informed consent was obtained from all subjects included in the study.

Study Design

Two random venous blood glucose samples with an interval of at least 2 weeks were obtained from patients in both groups. If a patient had a glucose level above 6.6 mmol/L, a further investigation with an oral glucose tolerance test (OGTT) was performed.

The OGTT was carried out as described by the World Health Organization (WHO) Study Group on Diabetes Mellitus.[27] After an overnight fast, the patients were given 75 g of glucose, dissolved in 250–300 mL of water and ingested within 5 minutes. During this test, the patients rested, fasted, and were not allowed to smoke. Capillary whole blood glucose concentrations were measured before and 2 hours after the glucose load.

The diagnoses of impaired glucose tolerance (IGT) and diabetes mellitus were based upon the result of the OGTT according to the WHO criteria.[27] The subjects were classified as having diabetes mellitus if the fasting capillary blood glucose value exceeded 6.7 mmol/L or if the 2-hour post-OGTT blood glucose value was above 11.0 mmol/L, and as having IGT if the fasting value was below 6.7 mmol/L and the 2-hour post-OGTT blood glucose value was between 7.8 and 11.0 mmol/L. A subject was also classified as having IGT if both random samples of blood glucose exceeded 10.0 mmol/L. The definition used for type 1 diabetes mellitus was that the patient required insulin treatment for survival. Such dependency was judged to be present if the patient presented with greatly raised concentrations of glucose and ketone bodies in the blood and urine and with typical symptoms such as increased thirst, polyuria, wasting, and, ultimately, stupor and coma.[27] All other subjects with diabetes mellitus were considered to have type 2 diabetes mellitus.

The following variables were registered for all patients: age, sex, body weight, height, drug therapy, duration of underlying disease, and history of diabetes in first-degree relatives. The subjects were asked directly about family history regarding diabetes, body weight, and height. In most cases, weight and height were confirmed by data from the medical records and by measuring these parameters. Information about age, sex, drug treatments, and duration of underlying disease was collected from the medical records. The onset of the psychiatric disease was defined as the first time the patient presented symptoms consistent with the diagnosis.

Analytical Methods

Single blood glucose concentrations in venous whole blood were analyzed by the beta-glucuronidase method on a Cobas Mira analyzer (Roche, Basel, Switzerland). In 53 of the patients treated with clozapine, serum levels of clozapine and its metabolites desmethylclozapine and clozapine-*N*-oxide were determined in our laboratory by a reversed-phase high-performance liquid chromatography technique based on a method published earlier.[28] In short, 1.0 mL of serum and 10 μL of a 20-μM solution of internal standard Lundbeck N-7084 (5-[pyrrolidinylpropyliden]-10,11-dihydro-5H-dibenso[a,d]cyklohepten; [Lundbeck A/S, Copenhagen, Denmark]) were mixed with 1.0 mL of 0.1 M sodium acetate buffer (pH = 6.8) and centrifuged. The supernatant was applied to an isolute HCX solid-phase column (Sorbent AB, Gothenburg, Sweden). After the sample was passed at a slow rate, the column was washed with 1 mL 1 M acetic acid and 2 mL methanol, and the desired compounds were then eluted with 2×0.75 mL of 2% NH_3 in methanol. After evaporation to dryness at 40°C, the compounds were dissolved in 500 μL of an eluent consisting of 58% acetonitrile, 22% methanol, and 20% K_2HPO_4. Thereafter, 20 μL of the eluate was injected onto an Apex CN RP analytical column (particle size = 5 μm; length = 150 mm; inner diam-

Table 1. Group Characteristics*

Characteristic	All Subjects: Clozapine Group (N = 63)			All Subjects: Control Group (N = 67)			All Subjects: p Value	Subjects With Diabetes Mellitus or IGT: Clozapine Group (N = 13)			Subjects With Diabetes Mellitus or IGT: Control Group (N = 6)			Subjects With Diabetes Mellitus or IGT: p Value
Male/female, N	36/27			41/26			.63	4/9			4/2			.25
Positive/negative heredity,[a] N	15/44			20/44			.59	4/8			3/3			.41
	Mean	SD	Range	Mean	SD	Range		Mean	SD	Range	Mean	SD	Range	
Age, y	41	9	22–65	48	10	25–65	< .001	46	11	33–65	55	11	36–65	.08
Body weight, kg	80	14	48–108	80	18	44–135	.99	75	17	48–104	83	8	70–90	.34
Height, cm	170	10	152–193	169	9	147–88	.48	166	8	155–178	166	10	152–178	.91
Body mass index, kg/m^2	27	4	18–41	28	6	15–40	.65	27	5	18–36	30	4	27–38	.23
Duration, y														
Disease[b]	15	9	0.5–37	21	9	0.3–45	< .001	16	10	2–36	31	11	13–36	.08
Treatment with current neuroleptic	3	1	0.1–6	8	6	0.2–22	< .001	3	1	0.5–5	6	6	1–17	.08

*Abbreviation: IGT = impaired glucose tolerance.
[a]Diabetes mellitus in parents, siblings, or children.
[b]Duration calculated from the first hospitalization when the patient was treated with a neuroleptic agent until September 1, 1995.

eter = 4.6 mm) with an Apex CN RP precolumn (particle size = 5 μm; length = 10 mm) (Jones Chromatography Ltd., Hengoed, U.K.). The limit of quantitation of the assay was 20 nmol/L of clozapine and its metabolites desmethylclozapine and clozapine-*N*-oxide. The method was linear for all analytes up to at least 3000 nmol/L. The coefficient of variance for intraassays and interassays ranged between 2% and 8% for these different analytes. Clozapine and its metabolites were analyzed using an ultraviolet detector with the wavelength set at 254 nm. Blood samples were drawn 10 to 18 hours after the last clozapine dose.

Statistical Analysis

Statistical evaluations were performed with Statistica software version 5 (Statsoft, Inc., Tulsa, Okla.) and included chi-square tests for dichotomous variables and unpaired Student t tests for continuous variables. A p value of less than .05 was considered statistically significant.

RESULTS

Characteristics of the subjects in each treatment group (clozapine vs. control) are summarized in Table 1. The 2 groups were similar with regard to body weight, height, body mass index, and sex, but subjects in the clozapine group were significantly younger ($p < .001$) and had a significantly shorter duration of disease ($p < .001$) and of neuroleptic treatment ($p < .001$).

None of the patients in either group had a diagnosis of diabetes mellitus or evidence of diabetes mellitus before the current neuroleptic treatment was initiated. In 8 of the 19 cases of type 2 diabetes mellitus or IGT, results of previously performed tests were available, and all these were normal. In the clozapine group, 21 (33%) of 63 presented with a blood glucose value higher than 6.6 mmol/L during treatment with clozapine, compared with 13 (19%) of 67 in the group treated with neuroleptics (Table 2). Seventeen

Table 2. Prevalence of Hyperglycemia, Type 2 Diabetes Mellitus, and IGT in Subjects Treated With Clozapine and in a Control Group of Subjects Treated With Conventional Depot Neuroleptics*

Condition	Clozapine Group N	Clozapine Group %	Control Group N	Control Group %	p Value
Hyperglycemia	21/63	33	13/67	19	.07
Type 2 DM	7/60	12	4/63	6	.30
IGT	6/60	10	2/63	3	.12
Type 2 DM or IGT	13/60	22	6/63	10	.06

*Abbreviation: DM = diabetes mellitus. Hyperglycemia was defined as a blood glucose concentration > 6.6 mmol/L.

of the 21 subjects in the clozapine group were investigated further with an OGTT. One subject refused OGTT but had 2 random glucose values above 10.0 mmol/L and was therefore classified as having IGT, and 3 subjects did not want to take part in the OGTT examination. In the control group, 4 of the 13 patients did not want to participate in an OGTT; thus, 9 were tested. None of the control subjects who refused to participate in an OGTT had presented 2 random blood glucose values above 10.0 mmol/L. Thirteen patients in the clozapine-treated group and 6 in the control group were classified as having type 2 diabetes mellitus or IGT (Table 3). Nine of 27 women treated with clozapine were classified as having type 2 diabetes mellitus or IGT compared with 2 of 26 in the control group.

There were no significant differences in clozapine dose or in serum concentrations of clozapine or its metabolites desmethylclozapine and clozapine-*N*-oxide between subjects classified as having IGT or type 2 diabetes mellitus and subjects with normal blood glucose levels (Table 4).

DISCUSSION

Of subjects treated with clozapine, 21.7% were classified as having type 2 diabetes mellitus or IGT. Of subjects

Table 3. Cases of Diabetes Mellitus and Impaired Glucose Tolerance*

Patient	Condition	Sex	Age (y)	Weight (kg)	Body Mass Index (kg/m^2)	Heredity[a] Type 2 Diabetes Mellitus	Disease[b]	Duration of Disease (y)	Blood Glucose Sample 1 (mmol/L)	Blood Glucose Sample 2 (mmol/L)	OGTT F-Glucose (mmol/L)	OGTT 2-hour Glucose (mmol/L)	Neuroleptic Treatment	Concomitant Medication
Subjects treated with clozapine (N = 13)														
1	Type 2 DM	F	36	70	27.3	1	Schizoaffective psychosis	13	6.5	7.8	10.1	16.3	Clozapine 500 mg/d	Levothyroxine, lithium
2	Type 2 DM	F	45	56	21.9	0	Schizophrenia	15	7.1	6.7	6.9	7.2	Clozapine 300 mg/d	Glibenclamide
3	Type 2 DM	M	44	104	32.8	0	Schizophrenia	2	12.4	9.0	8.0	13.8	Clozapine 300 mg/d	…
4	Type 2 DM	F	45	75	31.2	1	Schizophrenia	22	14.8	7.3	10.1	15.9	Clozapine 400 mg/d	…
5	Type 2 DM	F	53	96	35.7	1	Schizophrenia	11	5.4	7.5	5.5	14.2	Clozapine 200 mg/d	Ipratropium bromide, allopurinol, aspirin
6	Type 2 DM	F	59	71	27.1	?	Schizophrenia	29	10.4	8.7	3.0	12.7	Clozapine 25 mg/d	…
7	Type 2 DM	M	60	89	29.1	0	Schizophrenia	30	6.6	9.1	7.3	9.3	Clozapine 300 mg/d	…
8	IGT	M	34	93	29.4	0	Schizophrenia	5	12.0	11.1	…[c]	…[c]	Clozapine 500 mg/d	…
9	IGT	M	33	86	27.8	0	Schizophrenia	19	7.2	6.6	4.0	11.0	Clozapine 100 mg/d	Zuclopenthixol[d]
10	IGT	F	36	63	23.1	1	Schizophrenia	12	6.7	4.1	4.5	9.5	Clozapine 400 mg/d	…
11	IGT	F	42	48	17.6	0	Paranoid psychosis	14	7.9	7.0	5.5	8.6	Clozapine 300 mg/d	…
12	IGT	F	65	64	25.6	0	Schizophrenia	36	6.9	4.6	5.0	9.1	Clozapine 500 mg/d	…
13	IGT	F	40	66	26.4	0	Schizophrenia	5	7.6	5.8	4.9	7.4	Clozapine 400 mg/d	…
Subjects treated with depot neuroleptics (N = 6)														
1	Type 2 DM	F	36	70	27.3	1	Schizophrenia	13	18.8	11.9	7.9	16.2	Fluphenazine 19 mg/4w[e]	Diazepam, flunitrazepam, methixene
2	Type 2 DM	M	50	90	29.1	1	Schizophrenia	34	10.7	12.6	7.6	15.5	Flupenthixol 40 mg/4w[e]	Levomepromazine
3	Type 2 DM	M	59	80	30.1	0	Bipolar affective disorder	31	10.0	…[f]	7.2	16.4	Zuclopenthixol 100 mg/4w[e]	Lithium
4	Type 2 DM	M	65	78	27.6	1	Schizophrenia	?	14.6	13.6	14.6	20.6	Zuclopenthixol 200 mg/2w[e]	…
5	IGT	M	60	90	28.4	0	Paranoid psychosis	36	7.6	3.6	6.2	9.5	Zuclopenthixol 200 mg/4w[e]	…
6	IGT	F	62	88	38.1	0	Bipolar affective disorder	26	12.7	5.5	5.5	10.3	Zuclopenthixol 200 mg/3w[e]	Levomepromazine, methixene

*Abbreviations: F-Glucose = fasting blood glucose concentration, measured immediately before OGTT; OGTT = oral glucose tolerance test; 2-hour glucose = blood glucose concentration measured 2 hours after OGTT. Symbols: … = not applicable, ? = not known.
[a]0 = No case of diabetes mellitus in parents, siblings, or children; 1 = at least 1 case of diabetes mellitus in parents, siblings, or children.
[b]Disease = current diagnosis for which the subject is treated with neuroleptic medication.
[c]The subject did not want to participate in an oral glucose tolerance test.
[d]Oral treatment.
[e]Injection treatment with depot neuroleptic. Dose in mg per dosage interval.
[f]Only 1 blood glucose sample was drawn before the oral glucose tolerance test was performed.

treated with depot injections of neuroleptics, 9.5% were classified as having type 2 diabetes mellitus or IGT. Although the difference is not statistically significant, these observational data suggest an association between the treatment with clozapine and the appearance of alterations in glucose metabolism. To our knowledge, this is the first study that has dealt with this issue. Women were more often classified as having type 2 diabetes mellitus or IGT when treated with clozapine than when treated with conventional neuroleptics. The clinical significance of this finding is, however, difficult to assess because of the small numbers of subjects.

Previously, 8 cases (32-year-old man, 34-year-old woman, 41-year-old man, 42-year-old man, 44-year-old man, 46-year-old man, 51-year-old man, 51-year-old man) have been reported for which such an association between clozapine treatment and alterations in glucose metabolism has been suggested.[4–8] In contrast to our findings, how-

Table 4. Doses of Clozapine and Serum Concentrations of Clozapine and Its Metabolites Desmethylclozapine and Clozapine-*N*-Oxide

	Subjects With Type 2 DM or IGT				Subjects With Normal Blood Glucose Levels				
	N[a]	Mean	SD	Range	N[b]	Mean	SD	Range	p Value
Dose, mg/d	13	338	179	100–625	46	367	163	12.5–625	.59
Serum concentrations, nmol/L									
Clozapine	12	2151	1387	507–4888	40	1666	1257	27–5320	.50
Desmethylclozapine	12	1312	1037	207–2660	40	824	565	21–2748	.11
Clozapine-*N*-oxide	12	165	139	0–501	40	150	141	0–578	.85

[a]Analysis of clozapine and its metabolites was not performed in 1 subject due to practical reasons.
[b]A total of 47 subjects were classified as having normal blood glucose levels. Dose was not reported in 1 subject. Analysis of clozapine and its metabolites was not performed in 7 subjects due to practical reasons.

ever, many of these patients developed a type 1 diabetes mellitus after the start of clozapine treatment. Six of the 8 patients were black. In our study, only white patients participated.

If the criteria had been set according to that of the National Diabetes Data Group,[29] which uses a cutoff of 7.8 mmol/L instead of 6.7 mmol/L for the 2-hour blood glucose value of the OGTT, 2 fewer subjects in the clozapine group would be classified as having impairment of carbohydrate metabolism compared with the WHO criteria.[27]

The prevalence of diabetes mellitus in the general population in northern Sweden has been investigated in the Monica Project.[30] From these data, one should expect that the number of subjects with diabetes mellitus would be 2.1 in the clozapine-treated group (7 observed) and 3.4 in the control group (4 observed) when taking into account the age and gender distribution in the 2 groups. Thus, these data indicate that there is an excess occurrence of diabetes mellitus in the clozapine group, although the numbers involved are too small to make a generalization.

It has been suggested that diabetes mellitus is more common among schizophrenic patients than in the general population.[21–25] Among 95 schizophrenic patients in Italy, the prevalence of diabetes was 0% among patients younger than 50 years, 13% in patients 50 to 59 years old, and 19% in patients 60 to 69 years old.[25] These rates are considerably higher than those reported from population surveys in Italy. All cases were classified as type 2 diabetes mellitus. In that study, diabetes mellitus was more common in patients not receiving neuroleptics than in those patients who received such treatment.

The present study has a number of limitations. Data are observational, and since the number of cases with diabetes mellitus and IGT is low, the differences between the groups do not reach the level of .05 for usual statistical significance. The method of screening the populations by random blood samples may not be ideal. However, the screening method was feasible and probably contributed to make the dropout rate rather small: 3 of 63 in the clozapine group and 4 of 67 in the control group.

Potential biases also may have distorted the result. The fact that the 2 groups differed in various ways—for example, as regards to residence, age, duration of disease, and present neuroleptic treatment—could have had some impact on the prevalence of type 2 diabetes mellitus and IGT. The subjects in the clozapine group were younger, had a shorter duration of disease, and had been treated with the current neuroleptic agent for a shorter period of time than those in the control group. However, since the prevalence of diabetes increases with increasing age, one should expect a higher prevalence of type 2 diabetes mellitus and IGT in the oldest group, i.e., in the group of patients treated with depot neuroleptics, than in the clozapine group. Also a shorter exposure to the drug, as in the clozapine-treated group, should signify a decreased risk of developing a side effect such as diabetes mellitus compared with a longer drug exposure.

Another possibility is that the neuroleptic medication has already been discontinued in patients who have developed type 2 diabetes mellitus or IGT. This would lead to an underestimation of the risk to develop this adverse effect. Moreover, the occurrence of other adverse drug reactions that could have led to termination of the drug treatment might also suggest an underestimation of the risk. In fact, blood glucose concentrations were also studied in 10 of the total 26 patients who had either discontinued the clozapine treatment or moved from the area before the present study was performed. Before discontinuation, 4 of these subjects had at least 1 random blood glucose value above 10 mmol/L and 2 of them had undergone OGTT. One of these subjects could be classified as having type 2 diabetes mellitus and 1 as having IGT according to the result of the OGTT. Two of the 4 patients with hyperglycemia discontinued clozapine treatment because of granulocytopenia and agranulocytosis, respectively.

The pathophysiology of decreased glucose tolerance in clozapine users is unknown, but is presumably related to the pharmacologic properties of the drug. Weight gain during clozapine treatment is a well-recognized adverse effect[30] that may be related to altered glucose homeostasis.

The mechanism of weight gain remains to be established, but could be related to the noradrenergic and serotonergic antagonistic effects of clozapine or the drug's ability to alter plasma cortisol concentrations.[31] However, the body weights of the patients with IGT or type 2 diabetes mellitus in the clozapine group were not higher than in those showing normal glucose metabolism. In rats, results of in vivo and in vitro studies have suggested that chlorpromazine can produce a hyperglycemic response by suppression of insulin release.[18] Since clozapine and chlorpromazine share some properties regarding their receptor affinity profiles, it is possible that clozapine also can suppress insulin release.

In 2 of the patients who had terminated treatment with clozapine before the start of this study, both hyperglycemia (type 2 diabetes mellitus and IGT, respectively) and leukopenia (agranulocytosis and granulocytopenia, respectively) were observed concomitantly, suggesting a possible common mechanism. Desmethylclozapine, the major metabolite of clozapine, has been reported to be more toxic than clozapine itself. It has been suggested that this metabolite is involved in the pathophysiology of agranulocytosis,[32] although an additional vulnerability factor seems to be necessary. The levels of both parent compound and clozapine-*N*-oxide in our subjects classified as having IGT or type 2 diabetes mellitus were similar to those in the subjects with normal glucose homeostasis (Table 4). Interestingly, however, the concentration of desmethylclozapine tended to be higher in patients with type 2 diabetes mellitus and IGT than in patients in the normoglycemic group (Table 4). The difference, however, was not statistically significant.

In conclusion, this observational study indicates that subjects treated with clozapine might have an excess risk of developing hyperglycemia or diabetes mellitus compared with subjects treated with conventional depot neuroleptics. Physicians should be aware of this possible and potentially severe adverse effect. Since blood sampling already is performed in clozapine-treated subjects, monitoring of blood glucose concentrations would be easy and inexpensive to perform. However, conclusive recommendations as to how often and how long such monitoring should be performed cannot be given from our present data. Further studies of clozapine are needed to confirm these findings and to explain the possible mechanism leading to an increased susceptibility to diabetes or IGT.

Drug names: allopurinol (Zyloprim and others), amoxapine (Asendin), chlorpromazine (Thorazine and others), clozapine (Clozaril), diazepam (Valium and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), ipratropium bromide (Atrovent), levothyroxine (Synthroid and others), loxapine (Daxolin, Loxitane), perphenazine (Trilafon), salicylic acid (SalAc 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;45:789–795
2. Lieberman JA, Kane JM, Johns CA. Clozapine: guidelines for clinical management. J Clin Psychiatry 1989;50:329–338
3. Alvir JM, Lieberman JA, Safferman AZ, et al. Clozapine-induced agranulocytosis: incidence and risk factors in the United States. N Engl J Med 1993;329:162–167
4. Koval MS, Rames LJ, Christie S. Diabetic ketoacidosis associated with clozapine treatment. Am J Psychiatry 1994;151:1520–1521
5. Kamran A, Doraiswamy PM, Jane JL, et al. Severe hyperglycemia associated with high doses of clozapine [letter]. Am J Psychiatry 1994;151:1395
6. Peterson GA, Byrd SL. Diabetic ketoacidosis from clozapine and lithium cotreatment. Am J Psychiatry 1996;153:737–738
7. 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
8. Popli AP, Konicki PE, Jurjus GJ, et al. Clozapine and associated diabetes mellitus. J Clin Psychiatry 1997;58:108–111
9. Arnesson GA. Phenothiazine derivates and glucose metabolism. J Neuropsychiatry 1964;5:181–198
10. Thonnard-Neumann E. Phenothiazines and diabetes in hospitalized women. Am J Psychiatry 1968;124:978–982
11. Proakis AG, Mennear JH, Miya TS, et al. Phenothiazines-induced hyperglycemia: relation to CNS and adrenal effects. Proc Soc Exp Biol Med 1971;137:1385–1388
12. Dagli AJ. Severe hyperglycaemia following ingestion of chlorpromazine. J Assoc Physicians India 1984;32:762–763
13. Lambert AE, Henquin JC, Orci LO. Chlorpromazine in malignant insulinoma. BMJ 1972;3:701
14. Federspil G, Casara D, Stauffacher W. Chlorpromazine in the treatment of endogenous organic hyperinsulinism. Diabetologia 1974;10:189–191
15. Jori A, Carrara MC. On the mechanism of hyperglycemic effect of chlorpromazine. J Pharm Pharmacol 1966;18:623–624
16. Mennear JH, Miya TS. Chlorpromazine-induced glucose intolerance in the mouse. Proc Soc Exp Biol Med 1970;133:770–773
17. Wannarka GI, Fletcher HP, Maickel RP. Centrally mediated drug-induced hyperglycemia in mice. Neuropharmacology 1993;22:341–346
18. Ammon HPT, Orci L, Steinke J. Effect of chlorpromazine (CPZ) on insulin release in vivo and in vitro in the rat. J Pharmacol Exp Ther 1973;187: 423–429
19. Erle G, Basso M, Federspil G, et al. Effect of chlorpromazine on blood glucose and plasma insulin in man. Eur J Clin Pharmacol 1977;11:15–18
20. Tollefson G, Lesar T. Nonketotic hyperglycemia associated with loxapine and amoxapine: case report. J Clin Psychiatry 1983;44:347–348
21. Ward JL. Glucose tolerance in schizophrenia. Orthomolecular Psychiatry 1972;44:137–140
22. Dynes JB. Diabetes in schizophrenia and diabetes in nonpsychotic medical patients. Dis Nerv Syst 1969;30:341–344
23. McKee HA, D'Arcy PF, Wilson P. Diabetes and schizophrenia: a preliminary study. J Clin Hosp Pharm 1986;11:297–299
24. Brambilla F, Guastalla A, Guerrini A, et al. Glucose-insulin metabolism in chronic schizophrenia. Dis Nerv Syst 1976;37:98–103
25. Mukherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. Compr Psychiatry 1996;37:68–73
26. 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
27. WHO Study Group on Diabetes Mellitus. World Health Organisation Technical Reports series 727. Geneva, Switzerland: World Health Organization; 1985
28. Weigmann H, Hiemke C. Determination of clozapine and its major metabolites in human serum using automated solid-phase extraction and subsequent isocratic high-performance liquid chromatography with ultraviolet detection. J Chromatogr 1992;583:209–216
29. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979;28: 1039–1057
30. Stegmayr B, Asplund K. Diabetes as a risk factor for stroke: a population perspective. Diabetologia 1995;38:1061–1068
31. Leadbetter R, Shutty M, Pavalonis D, et al. Clozapine-induced weight gain: prevalence and clinical relevance. Am J Psychiatry 1992;149:68–72
32. Gerson SL, Arce C, Meltzer HY. N-desmethylclozapine: a clozapine metabolite that suppresses haemopoiesis. Br J Haematol 1994;86:555–561