The Effect of Clozapine on Factors Controlling Glucose Homeostasis

Oliver D. Howes, M.R.C.Psych.; Fiona P. Gaughran, F.R.C.P.I., M.R.C.Psych., M.D.; Stephanie A. Amiel, B.Sc., M.D., F.R.C.P.; Robin M. Murray, F.R.C.Psych., D.Sc.; and Lyn S. Pilowsky, M.R.C.Psych., Ph.D.

Background: This prospective study examines the effect of clozapine on factors determining glucose homeostasis.

Method: The sample consisted of all patients meeting DSM-IV criteria for schizophrenia who commenced clozapine treatment within the South London and Maudsley hospitals during 1 year (2000–2001). Growth hormone (GH), insulin-like growth factor-1 (IGF-1), and IGF binding protein-1 (IGFBP-1) were measured in 19 patients (10 female; mean age = 31.1 years [SD = 5.8]; 9 black British/African, 10 white British) before and after a mean of 2.5 (SD = 0.9) months of clozapine treatment.

Results: Baseline IGFBP-1 was low. IGFBP-1, GH, and IGF-1 were not significantly changed by clozapine treatment.

Conclusions: Clozapine does not alter GH, IGF-1, or IGFBP-1 within 3 months of commencing treatment, indicating that alteration in glucose tolerance associated with clozapine treatment involves other mechanisms yet to be elucidated. Baseline abnormalities in IGFBP-1 indicate a preexisting susceptibility to glucoregulatory dysfunction.

(J Clin Psychiatry 2004;65:1352–1355)

Received Dec. 17, 2003; accepted March 23, 2004. From the Division of Psychological Medicine, Institute of Psychiatry (Drs. Howes, Gaughran, Murray, and Pilowsky) and the Department of Diabetic Medicine, GKT School of Medicine, King's College (Dr. Amiel), London, United Kingdom.

Financial support for this study was provided by the Stanley Medical Research Institute, Bethesda, Md.

Dr. Howes has previously received charitable, unrestricted research grants from AstraZeneca and Eli Lilly. Dr. Gaughran has been a speaker/advisory board member for Bristol-Myers Squibb, Janssen-Cilag, and AstraZeneca; has received an honorarium from AstraZeneca; and has a family member who works for Eli Lilly. Dr. Murray has received honoraria from Bristol-Myers Squibb, Janssen, Pfizer, Eli Lilly, and AstraZeneca. Dr. Pilowsky is a U.K. Medical Research Council Senior Fellow and has received investigator-led charitable research grants from Novartis, AstraZeneca, Janssen, and Sanofi-Synthelabo.

The authors thank David Taylor; Brian Smith; the staff of the Pharmacy and Pathology Departments, Maudsley Hospital; the Medical Toxicology Department, Guy's Hospital; and Rebecca Walwyn, Department of Biostatistics, Institute of Psychiatry.

Corresponding author and reprints: Oliver Howes, M.R.C.Psych., Box 63, Division of Psychological Medicine, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London, SE5 8AF, United Kingdom (e-mail: O.Howes@iop.kcl.ac.uk).

Clozapine shows unique efficacy, has reduced rates of extrapyramidal side effects compared to typical antipsychotics, and is the only antipsychotic licensed for treatment-resistant schizophrenia.[1] There is, however, increasing evidence linking clozapine treatment with hyperglycemia. Three hundred eighty-four cases of abnormal glucose control associated with clozapine have been reported up until 2000.[2] The majority of such cases occur within 3 months of beginning clozapine therapy.[2] Two retrospective studies found that clozapine treatment was associated with an increased relative risk of diabetes compared with conventional antipsychotics,[3,4] and another found no significant association.[5]

Experimental studies confirm an adverse effect of clozapine on glucose tolerance. In a cross-sectional study, impaired glucose tolerance or frank diabetes mellitus was twice as common in patients taking clozapine compared to patients taking other antipsychotics.[6] A study of patients taking clozapine over a 5-year period found that over one third developed diabetes.[7] Clozapine is associated with significantly higher glucose levels on oral glucose tolerance testing than typical antipsychotics.[8] Clozapine treatment has been found to be associated with the development of abnormal glucose control in 55% of patients and to significantly increase fasting glucose levels within 3 months.[9]

The control of blood glucose levels is complex, involving interaction between hormones, binding proteins, and target tissues. Insulin, insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-1 (IGFBP-1), and growth hormone (GH) are important glucoregulatory factors.[10–13] Insulin and IGF-1, which has functional similarities to insulin, act to reduce blood glucose levels.[11,12] Low levels of IGF-1 are associated with an increased risk of subsequent abnormal glucose control and are inversely related to glucose levels measured using an oral glucose tolerance test (OGTT).[10] IGFBP-1 is the main binding protein, which acts to reduce the activity of IGF-1, counteracting the hypoglycemic effect of IGF-1, and is linked with glucose intolerance.[12] GH hypersecretion is associated with diabetes mellitus and is linked to weight gain, insulin resistance, and the development of diabetic microvascular complications.[13] GH secretion in

those with and without diabetes increases hepatic glucose output and decreases peripheral glucose use, acting to increase blood glucose levels.[13]

It has been suggested that clozapine acts to cause abnormal glucose control by disturbing the complex factors governing glucose-insulin homeostasis.[3,14] Despite findings of marked alterations in glucose control associated with clozapine treatment, insulin levels and insulin resistance were not altered by clozapine treatment,[9] suggesting that clozapine may act to reduce glucose tolerance through other regulatory factors. IGF-1 levels have been found to be significantly lower in patients taking clozapine compared to patients taking classical antipsychotics, leading Melkersson et al.[15] to hypothesize that GH levels are abnormal in patients taking clozapine. Patients taking clozapine do not show the inverse relationship between IGFBP-1 and insulin levels found in healthy controls.[15] Although these findings are compatible with the hypothesis that clozapine alters glucose-insulin homeostasis, causality cannot be assumed from cross-sectional studies.

No study has assessed IGF-1, IGFBP-1, and GH levels prospectively, at baseline and again following initiation of clozapine, to establish whether abnormalities in these factors are related to clozapine treatment. If clozapine alters IGF-1, IGFBP-1, and GH levels, this would further understanding of the mechanism by which clozapine affects glucose control and weight. We have previously reported the development of marked glucose intolerance without significant changes in insulin levels after clozapine treatment for 3 months.[9] We have therefore gone on to test 3 hypotheses that could explain the alteration in glucose tolerance associated with clozapine treatment over this time period: (1) clozapine treatment is associated with a reduction in IGF-1 levels, (2) clozapine treatment is associated with an elevation in IGFBP-1 levels, and (3) clozapine treatment is associated with an elevation in GH levels.

METHOD

The study design and sample characteristics have been described elsewhere.[9] The South London and Maudsley NHS Trust local research ethics committee approved the study. In brief, all DSM-IV–diagnosed patients with schizophrenia within the catchment area starting clozapine treatment during a 1-year period from 2000 to 2001 were invited to participate. After complete description of the study to the subjects, written informed consent was obtained. The assessment was performed at baseline, before commencing clozapine, and repeated after a mean 2.5 months (SD = 0.9) of clozapine treatment.

Assessment

A fasting blood sample was taken for the measurement of GH, IGF-1, and IGFBP-1 levels. GH and IGF-1 were analyzed using the Nichols Advantage automated chemiluminescence immunoassay system (Nichols Institute Diagnostics, San Clemente, Calif.). Fasting status was confirmed by nursing staff, glucose level measurement, and careful questioning of patients. Assessment was rescheduled if there was doubt as to a subject's fasting status. IGFBP-1 was assayed manually using ELISA kits (Medix Biochemica, Kauniainen, Finland). Within- and between-assay variation was < 6% for GH values < 6.1 mU/L (sensitivity = 0.3 mU/L), < 7.5% for IGF-1 values < 106 nmol/L (sensitivity = 0.8 nmol/L), and < 7.5% for IGFBP-1 values < 118 µg/L (sensitivity = 0.4 µg/L). Body mass index (BMI = weight [kg]/height^2 [m]), diet, and medications were recorded. Clozapine and norclozapine levels were measured using high performance liquid chromatography (within- and between-assay precision across the concentration range was < 6% and < 5%, respectively, for clozapine and < 7.5% and < 5.5%, respectively, for norclozapine, and assay sensitivity was 0.01 mg/L for both).[16]

Data Analysis

Paired sample t tests were used to compare mean IGF-1, IGFBP-1, and GH levels preclozapine and postclozapine treatment. Correlations between measures of insulin homeostasis and clozapine and norclozapine levels were tested using Pearson's product moment correlation.

RESULTS

Nineteen subjects completed the study (10 female; mean age = 31.1 (SD = 5.8); 9 black British/African, 10 white British). Mean dose of clozapine at follow-up was 344 mg/day (SD = 101), and mean serum levels of clozapine and norclozapine were 0.44 mg/L (SD = 0.21) and 0.24 mg/L (SD = 0.09), respectively. Medications taken by patients at baseline were as follows: olanzapine (N = 9, 1 in combination with zuclopenthixol), amisulpride (N = 1), quetiapine (N = 1), risperidone (N = 4), zuclopenthixol (N = 3, 1 in combination with olanzapine), sulpiride (N = 2), venlafaxine (N = 4), paroxetine (N = 1), fluoxetine (N = 2), orphenadrine (N = 2), procyclidine (N = 2), carbamazepine (N = 1), lithium (N = 1), sodium valproate (N = 1), beclomethasone inhaler (N = 1), and omeprazole (N = 1).

Table 1 shows the BMI, GH, IGF-1, and IGFBP-1 levels preclozapine and postclozapine. There were no significant differences in GH, IGF-1, or IGFBP-1 before and on clozapine treatment: GH ($t = 1.8$, $df = 15$, $p = .088$), IGF-1 ($t = 0.58$, $df = 15$, $p = .57$), and IGFBP-1 ($t = 1.2$, $df = 15$, $p = .24$). There was no correlation between change in BMI, clozapine and norclozapine blood levels, and GH ($p = .14$, $p = .7$, $p = .06$, respectively), IGF-1 ($p = .88$, $p = .5$, $p = .6$, respectively), or IGFBP-1 ($p = .15$, $p = .5$, $p = .4$, respectively) levels on clozapine treatment.

Table 1. Difference Between Mean Values of Factors Controlling Glucose Homeostasis at Baseline and Follow-Up After Clozapine Treatment

Factor	Baseline, Mean (SD)	Follow-Up, Mean (SD)	Change	95% CI
BMI (kg/m^2)	28.9 (7.2)	29.7 (6.8)	+0.8	+1.69 to –0.39
IGF-1 (nmol/L)	25.5 (8.7)	24.7 (9.1)	–0.8	–2.18 to 3.81
IGFBP-1 (μg/L)	3.1 (3.7)	2.4 (2.8)	–0.7	–0.41 to 1.55
GH (mU/L)	1.1 (1.7)	0.6 (1.1)	–0.5	–0.13 to 1.69

Abbreviations: BMI = body mass index, CI = confidence interval, GH = growth hormone, IGF = insulin-like growth factor, IGFBP = IGF binding protein.

DISCUSSION

This is the first direct evidence that clozapine treatment does not alter IGF-1, IGFBP-1, and GH, despite being associated with increased glucose levels in this sample (mean increases of 0.55 mmol/L [p = .01] and 1.4 mmol/L [p = .002] for fasting and 2-hour post-carbohydrate load glucose levels, respectively).[9] The present findings refute our initial hypotheses that the alteration in glycemic control is due to changes in glucose homeostatic factors (see introduction) and have important implications for the mechanism by which clozapine affects glucose control. The findings extend previous research by indicating that clozapine does not act to cause glucose intolerance through alterations in these measures of glucose-insulin homeostasis, and do not support the hypothesis suggested by Melkersson et al.[15] that clozapine alters GH secretion. Additionally, IGF-1 and GH levels were within the normal population range.[10,11] IGFBP-1 levels were low, however, compared with normal population data and the levels reported by Melkersson et al.[15] for patients taking clozapine. Low IGFBP-1 levels are consistent with preexisting elevated insulin levels,[10] suggesting insulin resistance, and have been reported in patients taking other antipsychotics.[17]

Methodological Considerations

It is possible that the sample size was insufficient to detect alterations. It is, however, larger than previous samples[15] and has > 99% power to detect a change of 1 SD, which is the difference in IGF-1 levels between patients taking clozapine and other antipsychotics previously reported in the literature.[15] It could be that the time frame was too short to detect changes. Previous studies, however, indicate that the effect of clozapine on glucose control occurs rapidly, within months of commencing treatment. Therefore, if changes in GH, IGF-1, or IGFBP-1 cause alterations in glucose control, then alterations should occur over the period of our study. The effect of diurnal variation on the endocrine results was minimized by taking samples at the same time of day. As GH secretion is pulsatile, one-off sampling may be less informative than repeated sampling of GH.[13] Although this is unlikely to explain the lack of differences between the 2 time points, the risk of a type II error is increased and studies using repeated sampling may be warranted. The low IGFBP-1 levels indicate a preexisting abnormality, which may be related to current medication. This does not, however, alter the key finding, as the sample was clinically representative of patients commencing clozapine.

Implications

The results indicate that the mechanism by which clozapine alters glucose control is independent of GH, IGF-1, and IGFBP-1, and suggest a direct effect such as an alteration in central glucose sensing. Clozapine has been reported to affect central glucose regulation.[18,19] Such an effect would be consistent with the relatively rapid onset of elevated glucose levels independent of changes in IGF-1, IGFBP-1, and GH. A further implication of these findings is the evidence of baseline abnormalities in IGFBP-1, which may reflect prior antipsychotic treatment effects or a pathophysiologic effect of schizophrenia.

Future work is now indicated, correlating GH, IGF-1, and IGFBP-1 levels with glucose and insulin levels and investigating whether the low IGFBP-1 levels reported in the sample prior to commencing clozapine are secondary to prior antipsychotic treatment or other factors. Further follow-up may indicate whether there are longer-term effects of clozapine on GH, IGF-1, and IGFBP-1.

Clozapine is a uniquely efficacious treatment but can be associated with the development of diabetes mellitus. The results of this study indicate that glucose elevation is not through alterations in the GH, IGF-1, or IGFBP-1 control of glucose homeostasis, but may be through other actions intrinsic to the drug.

Drug names: beclomethasone inhaler (Vanceril and others), carbamazepine (Carbatrol, Tegretol, and others), clozapine (Clozaril, Fazaclo, and others), fluoxetine (Prozac and others), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), omeprazole (Prilosec and others), orphenadrine (Norflex and others), paroxetine (Paxil and others), procyclidine (Kemadrin), quetiapine (Seroquel), risperidone (Risperdal), sodium valproate (Depacon and others), venlafaxine (Effexor).

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. Koller E, Schneider B, Bennett K, et al. Clozapine-associated diabetes. Am J Med 2001;111:716–723
3. Sernyak MJ, Leslie DL, Alarcon RD, et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. Am J Psychiatry 2002;159:561–566
4. Lund BC, Perry PJ, Brooks JM, et al. Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension: a claims-based approach. Arch Gen Psychiatry 2001;58:1172–1176
5. Wang PS, Glynn RJ, Ganz DA, et al. Clozapine use and risk of diabetes mellitus. J Clin Psychopharmacol 2002;22:236–243
6. 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
7. 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
8. Newcomer JW, Haupt DW, Fucetola R, et al. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. Arch Gen Psychiatry 2002;59:337–345
9. Howes OD, Bhatnagar A, Gaughran FP, et al. A prospective study of impairment in glucose control caused by clozapine without changes in insulin resistance. Am J Psychiatry 2004;161:361–363
10. Sandhu MS, Heald AH, Gibson JM, et al. Circulating concentrations of insulin-like growth factor-I and development of glucose intolerance: a prospective observational study. Lancet 2002;359:1740–1745
11. Nyomba BL, Berard L, Murphy LJ. Free insulin-like growth factor I (IGF-I) in healthy subjects: relationship with IGF-binding proteins and insulin sensitivity. J Clin Endocrinol Metab 1997;82:2177–2181
12. Lewitt MS. Role of the insulin-like growth factors in the endocrine control of glucose homeostasis. Diabetes Res Clin Pract 1994;23:3–15
13. Holt RI, Simpson HL, Sonksen PH. The role of the growth hormone-insulin-like growth factor axis in glucose homeostasis. Diabet Med 2003; 20:3–15
14. Lund BC, Perry PJ, Brooks JM, et al. Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension: a claims-based approach. Arch Gen Psychiatry 2001;58:1172–1176
15. 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
16. McCarthy PT, Hughes S, Paton C. Measurement of clozapine and norclozapine in plasma/serum by high performance liquid chromatography with ultraviolet detection. Biomed Chromatogr 1995;9:36–41
17. Melkersson KI, Hulting A-L, Brismar KE. Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. J Clin Psychiatry 2000;61:742–749
18. Dwyer DS, Pinkofsky HB, Liu Y, et al. Antipsychotic drugs affect glucose uptake and the expression of glucose transporters in PC12 cells. Prog Neuropsychopharmacol Biol Psychiatry 1999;23:69–80
19. Ardizzone TD, Bradley RJ, Freeman AM III, et al. Inhibition of glucose transport in PC12 cells by the atypical antipsychotic drugs risperidone and clozapine, and structural analogs of clozapine. Brain Res 2001;923: 82–90

