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The effect of clozapine on factors controlling glucose homeostasis

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Abstract

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

Method—The sample consisted of all patients commencing clozapine within the South London and Maudsley hospitals during one year. 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 (SD: 5.8); 9 black British/ African, 10 white British) before, and after, an average 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, or IGFBP-1 within three 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 pre-existing susceptibility to glucoregulatory dysfunction.

Keywords

clozapine; diabetes mellitus; glucose control; IGF; GH

INTRODUCTION

Clozapine shows unique efficacy, reduced rates of extra-pyramidal 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 hyperglycaemia. 384 case reports of abnormal glucose control associated with clozapine have emerged in the last 8 years[2]. The majority of such cases occur within three months of beginning clozapine[2]. Two retrospective studies found clozapine treatment was associated

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with an increased relative risk of diabetes compared with conventional antipsychotics[3;4], and one 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 five year period found 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 significantly increased 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 OGTT[10]. IGFBP-1 is the main binding protein which acts to reduce the activity of IGF-1, counteracting the hypoglycaemic 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]. This suggests 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* to hypothesise that GH levels are abnormal in patients taking clozapine[15]. 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 associated with commencing clozapine treatment[9]. We have therefore gone on to test three hypotheses that could explain the alteration in glucose tolerance associated with clozapine treatment:

1. clozapine treatment is associated with a reduction in IGF-1 levels
2. clozapine treatment is associated with an elevation in IGFBP-1 levels
3. clozapine treatment is associated with an elevation in GH levels.

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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 patients within the catchment area starting clozapine during 2000-2001 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. GH and IGF-1 were analysed using the Nichols Advantage automated chemiluminescence immunoassay system, Nichols Institute Diagnostics, 2002. IGFBP-1 was assayed manually using ELISA kits (Medix Biochemica IGFBP-1, Diagenics, 2002). 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 0.01mg/l for both)[16].

DATA ANALYSIS

Paired sample t-tests were used to compare mean IGF-1, IGFBP-1, and GH levels pre and post clozapine 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 344mg (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.

Table 1 shows the BMI, GH, IGF-1 and IGFBP-1 levels pre and post clozapine. There were no significant differences in GH, IGF or IGFBP-1 before and on clozapine treatment: GH (t=1.8, df= 15, p=0.088), IGF-1 (t=0.58, df=15, p=0.57), and IGFBP-1 (t=1.2, df=15, p=0.24). There was no correlation between change in BMI, clozapine and norclozapine blood levels and GH (p=0.14, p=0.7, p=0.06 respectively), IGF-1 (p=0.88, p=0.5, p=0.6 respectively), or IGFBP-1 (p=0.15, p=0.5, p=0.4 respectively) levels on clozapine.

DISCUSSION

This is the first direct evidence that clozapine treatment does not alter IGF-1, IGFBP-1 and GH, despite, as previously reported, a highly significant increase in glucose levels during the course of clozapine treatment [9]. The present findings refute our initial hypotheses that this 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's *et al* that clozapine alters GH secretion[15].

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Additionally IGF-1 and GH levels were within the normal population range[10;11]. IGFBP-1 levels were low, however, compared to normal population data and the levels reported for patients taking clozapine by Melkersson *et al*[15]. Low IGFBP-1 levels are consistent with pre-existing 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, however, it is larger than previous samples, and has >99% power to detect a change of 1 SD[15]. It could be 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, IGFBP-1 cause alterations in glucose control, then alterations should occur over the period of our study. As GH secretion is pulsatile, one-off sampling may be less informative than repeated sampling[13]. Although this is unlikely to explain the lack of differences between the two 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 pre-existing 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 suggests 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 changes 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 pathophysiological 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 this is not through alterations in the GH, IGF or IGFBP-1 control of glucose homeostasis, but may be through other actions intrinsic to the drug.

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Reference List

1. Kane J, Honigfeld G, Singer J. Clozapine for treatment resistant schizophrenia: a double-blind comparison with chlorpromazine. Archives of General Psychiatry. 1988; 45:789–796. [PubMed: 3046553]
2. Koller E, Schneider B, Bennett K, et al. Clozapine-associated diabetes. Am J Med. 2001; 111:716–723. [PubMed: 11747852]

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. [PubMed: 11925293]

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. [PubMed: 11735847]

5. Wang PS, Glynn RJ, Ganz DA, et al. Clozapine use and risk of diabetes mellitus. J Clin Psychopharmacol. 2002; 22:236–243. [PubMed: 12006892]

6. Hagg S, Joelsson L, Mjorndal 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. [PubMed: 9671341]

7. Henderson DC, Cagliero E, Gray C. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five year naturalistic study. American Journal of Psychiatry. 2000; 157:975–981. [PubMed: 10831479]

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. [PubMed: 11926934]

9. Howes OD, Bhatnagar A, Gaughran FP, Amiel SA, Murray RM, Pilowsky LS. Clozapine causes impaired glucose control without changes in insulin resistance- a prospective study. Am.J Psychiatry. 2003 In Press.

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. [PubMed: 12049864]

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. [PubMed: 9215291]

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. [PubMed: 7516850]

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. [PubMed: 12519314]

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. [PubMed: 11735847]

15. Melkerson KI, Hulting AL, Brismar KE. Different influences of classical antipsychotics and clozapine on glucose-insulin homeostasis in patients with schizophrenia or related psychoses. Journal of Clinical Psychiatry. 1999; 60:783–791. [PubMed: 10584769]

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. [PubMed: 7734932]

17. Melkersson KI, Hulting AL, 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. [PubMed: 11078035]

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. [PubMed: 10368857]

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. [PubMed: 11743975]

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Table 1

Showing no difference between mean values of factors controlling glucose homeostasis at baseline and follow-up after clozapine treatment.

	Baseline (SD)	Follow-up (SD)	95 % Confidence interval
BMI (kg/m^2)	28.9 (7.2)	29.72 (6.8)	+1.69 to −0.39
IGF 1 (nmol/l)	25.5 (8.7)	24.7 (9.1)	−2.18 to 3.81
IGFBP 1 (μg/l)	3.1 (3.7)	2.4 (2.8)	−0.41 to 1.55
GH (mU/l)	1.1 (1.7)	0.61 (1.1)	−0.13 to 1.69