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A prospective study of impairment in glucose control caused by clozapine without changes in insulin resistance

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Abstract

Objectives—This prospective study examines the effect of clozapine on glucose control and insulin sensitivity.

Method—Glucose homeostasis was measured in 20 patients (mean age 30.5 yrs (SD: 7.4), 45% female) before, and after, a mean 2.5 (SD: 0.95) months of clozapine treatment. Oral glucose tolerance test (OGTT), and insulin levels were measured. Insulin resistance was assessed using the homeostasis model assessment (HOMA-IR).

Results—55% of subjects developed abnormal glucose control (n=11, mean age 30.2 (SD: 7.1), 46% female). Patients showed insulin resistance at baseline (mean HOMA-IR level=3.88, SD=2.93), which was unaffected by clozapine (p=0.37). Mean fasting and 2-hour glucose levels increased by 0.55 mmol/l (p=0.01) and 1.4mmol/l (p=0.002) respectively.

Conclusions—Clozapine impairs glucose control within four months of treatment, independent of changes in insulin sensitivity and BMI.

Introduction

Clozapine shows a unique profile of treatment efficacy but cross-sectional and naturalistic studies link clozapine treatment to hyperglycemia, and an increased relative risk of diabetes, [1-3].

Clozapine treatment has been associated with elevated insulin levels when compared to patients taking typical antipsychotics, suggesting that clozapine induces insulin resistance[2].

Glucose-insulin homeostasis has not been previously evaluated prospectively, before and following clozapine treatment. Therefore we tested the hypotheses that:

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1. Clozapine treatment is associated with the development of abnormal glucose tolerance (as measured by an OGTT).
2. Clozapine treatment is associated with the development of insulin resistance (measured by HOMA-IR).

Methods

Subjects

The South London and Maudsley NHS Trust research ethics committee approved the study. All patients within the hospitals' catchment area intending to start clozapine during 2000-2001 were invited to participate. After complete description of the study to the subjects, written informed consent was obtained.

Inclusion criteria were: DSM-IV diagnosis of schizophrenia, switching to sole antipsychotic treatment with clozapine. Exclusion criteria were: diabetes mellitus, treatment for glycemic control, and conditions associated with glucose intolerance.

28 patients had baseline assessments and commenced clozapine. Four dropped out (hypotensive reactions), and 2 declined to participate further. In the remaining subjects, the mean age was 30.5 yrs (SD 7.4), 11 were female, 11 male, 11 black African/ African-Caribbean and 11 white British. 16 smoked and 17 drank alcohol (all <21units/week).

Four patients had a family history of diabetes (first degree relative, n=1; second degree relative, n=3). Patients consumed a standard diet containing >150g carbohydrate/day, and all but two were in-patients throughout the study.

Procedure

Subjects received a baseline assessment in the week prior to commencing clozapine. Clozapine dose was titrated according to clinical response. Subjects were followed up after two to four months of treatment (mean: 2.5 months (SD: 0.95 month)).

At follow-up, the measures carried out at baseline were repeated, and clozapine levels measured.

Assessment

A standard OGTT was performed according to World Health Organisation (WHO) specifications [4]. Subjects fasted under observation from mid-night before the test. Venous blood samples were taken at 9am to measure fasting plasma glucose, insulin and clozapine levels. Subjects then drank 75g anhydrous glucose in 300ml of water within 5 minutes, and venous blood samples were taken after 30 minutes (confirming glucose absorption), and 2-hours. Plasma glucose was measured using an enzymatic reference assay (Cobas Integra 400, Roche Diagnostics), and classified according to WHO criteria[4]. Insulin was assayed using an ELISA kit (Mercodia Iso Insulin ELISA, Diagenics). Body mass index (BMI=weight (kg)/ height^2 (m)), diet, and medications were recorded.

Insulin resistance was evaluated using the HOMA-IR method: HOMA-IR= [fasting insulin (μU/ml) × fasting glucose (mmol/l)]/ 22.5[5]. Clozapine levels were measured using high performance liquid chromatography.

Data analysis

Paired sample t-tests were used to compare mean fasting glucose, HOMA-IR, and 2-hour glucose levels pre and post clozapine treatment. The 2-hour glucose levels were adjusted using simple linear regression (dependent variable: change in 2-hour glucose level, independent variable: change in fasting glucose level). The McNemar test for paired proportions was used to compare the ratio of abnormal to normal OGTT results before and after clozapine treatment. Correlations between change in BMI and change in fasting and 2-hour glucose levels were tested using Pearson's product moment correlation.

Results

Two patients were diabetic at baseline and excluded. Of the remaining 20, 11 (55%) developed de novo abnormal glucose tolerance on OGTT measurement (1 diabetes mellitus, 8 impaired glucose tolerance, 2 impaired fasting glycemia). There was a highly significant increase in the proportion of patients showing abnormal glucose control following clozapine compared to before treatment (McNemar test: p=0.006). Table 1 shows baseline and follow-up levels for the outcome measures. Mean fasting glucose level increased by 0.55 mmol/l (t=−2.9, df=19, p=0.01), and mean 2-hour glucose level by 1.4mmol/l (t=−3.5, df=19, p=0.002), which remained significant after adjusting for fasting glucose (t=−3.2, df=19, p=0.005). There was no significant change in insulin (t=0.128, df=14, p=0.9), or HOMA-IR levels (t=−0.9, df=14, p=0.37). Mean BMI increased by 0.82 kg/m^2, although this was not significant (t=−1.325, df=17, p=0.2), and there was no correlation between change in BMI and change in fasting (r=0.17, p=0.49) or 2-hour glucose levels (r=0.37, p=0.14).

Medications at baseline were: olanzapine, n=10, amisulpride, n=1, quetiapine, n=1, risperidone, n=3, zuclopenthixol, n=3, sulpiride, n=2, venlafaxine=4, paroxetine=1, fluoxetine=2, orphenadrine= 2, procyclidine= 2, carbamazepine=1, lithium=1, sodium valproate=1, beclomethasone inhaler=1 and omeprazole=1.

At follow-up the mean clozapine dose was 341 mg/day (SD 105.4), and the mean clozapine blood levels was 0.42 mg/l (SD 0.21). Apart from switching antipsychotic to clozapine, there were no changes in patients' drug regimens from baseline.

Discussion

This is the first direct evidence that, within four months, clozapine treatment results in increased plasma glucose concentrations, independent of changes in insulin resistance or BMI. Clozapine treatment was associated with a 0.65-0.85 S.D. change in glucose concentration, and the onset of abnormal glucose tolerance in 55% of patients as assessed by OGTT. This study extends previous findings[1-3] by indicating that de novo glucose control abnormalities are common within months of clozapine initiation in a group screened to exclude pre-existing diabetes. Thus, it provides evidence for a causal relationship between clozapine treatment and the development of hyperglycemia.

Baseline BMI was in the overweight range (25-30 kg/m^2), consistent with previous studies of patients commencing clozapine[1]. The baseline HOMA-IR level was within the upper quintile of the range of HOMA-IR levels seen in healthy controls, indicating an increased risk of developing diabetes[5]. The similarity of HOMA-IR levels with previous reports[3] suggests that patients show a pre-existing insulin insensitivity that may be related to prior treatment, schizophrenia, or raised BMI.

It is possible that the development of hyperglycemia is unrelated to clozapine treatment, and may be incidental or secondary to concomitant medication. However, concomitant

medications were unaltered, and the short time span, and magnitude of the changes make it unlikely that we are observing the natural development of abnormal glucose control: <5% of patients taking olanzapine developed hyperglycemia over >2years follow-up[2].

Potential explanatory mechanisms

HOMA-IR levels did not show significant increases, which refutes the initial hypothesis that changes in glucose control following clozapine treatment are due to increased insulin resistance. BMI did not significantly increase. We did not measure changes in body composition, however these characteristically influence glucose homeostasis through altered insulin sensitivity[6]. An alternative mechanism would be a direct drug effect on glucose regulation. Clozapine reduces glucose uptake in neuronal cells[7]. This would reset the plasma glucose levels that glucose sensing neurones accept as normal, meaning the glucose level is perceived as lower than it is, thus resulting in compensatory increases in glucose levels. This mechanism would explain the rapid increase in plasma glucose level independent of changes in HOMA-IR levels.

Our results indicate that patients taking clozapine are at increased risk of developing abnormal glucose control. Diabetes mellitus is a leading cause of morbidity, and patients with mental disorders frequently do not receive appropriate diabetic care[1;6]. There have been cases of diabetic keto-acidosis and death following clozapine treatment[3]. Furthermore, hyperglycemia below the threshold for diagnosing diabetes is associated with increased risk of cardio-vascular complications[6]. Clinicians will need to weigh these issues in the balance when deciding to initiate clozapine.

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Table 1

mean values at baseline and follow-up, and the 95% confidence interval of the difference between the means.

	Baseline (SD)	Follow-up (SD)	Confidence interval
Fasting glucose (mmol/l)	5.05 (0.7)	5.60 (0.9)	+0.94 to +0.15
2 hour glucose (mmol/l)	5.94 (1.52)	7.27 (2.4)	+2.13 to +0.53
Insulin (pmol/l)	101.6 (70.2)	110.3 (105.2)	+29.5 to −33.2
HOMA-IR	3.88 (2.93)	4.83 (4.8)	+0.18 to −0.44
Weight (kg)	82.4 (24.7)	85.5 (23.6)	+0.47 to −1.3
BMI (kg/m^2)	28.9 (7.2)	29.72 (6.8)	+1.69 to −0.39