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A prospective study of glycaemic status in anti-psychotic-treated patients

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Abstract

Anti-psychotic drugs, particularly the second generation, or 'atypical' agents, have been implicated in the development of metabolic dysfunction such as diabetes mellitus. There is a paucity of longitudinal data on the natural history of glucose homeostasis in anti-psychotic-treated patients, and there are no universally accepted strategies for managing worsening glycaemic control in this population. Notwithstanding, several guidelines recommend switching to a 'lower risk' agent if patients develop worsening glycaemic control during anti-psychotic treatment. We prospectively followed a cohort of 106 anti-psychotic-treated patients from across the diagnostic spectrum, and investigated changes in glycaemic status. Between baseline and follow-up assessment (mean follow-up time, 599.3 [SD ± 235.4] days glycaemic status was unchanged in 78 (86.7%) patients; 5 (5.6%) reverted from impaired fasting glucose (IFG) to normoglycaemia in the absence of any pharmacological or lifestyle intervention and all were taking a 'high risk' drug (clozapine or olanzapine). These preliminary data suggest that progression to overt diabetes mellitus is not inevitable in patients who develop IFG during anti-psychotic treatment. Switching to another agent simply on the basis of the development of IFG may not offer any advantage, especially if the mental state is stable.

Keywords

anti-psychotics, diabetes, impaired fasting glucose, schizophrenia, bipolar disorder, body mass index

Introduction

Current evidence is increasingly pointing to an association between anti-psychotic drug use and metabolic dysfunction such as obesity and disorders of glucose homeostasis (Consensus Development Conference, 2004; Newcomer and Haupt, 2006). However, a causative link between diabetes and anti-psychotic drugs has yet to be established (Holt and Peveler, 2006) and pathophysiological mechanisms underpinning anti-psychotic-related metabolic dysfunction remain to be elucidated. Despite the paucity of head-to-head prospective studies comparing the incidence of diabetes in patients treated with anti-psychotics, it has been suggested that individuals developing worsening glycaemic control whereas treated with an agent with a 'high-risk' of causing abnormalities of glucose homeostasis (e.g., olanzapine or clozapine) should be switched to an agent 'that has not been associated with significant weight gain or diabetes' (Consensus Development Conference, 2004).

As part of a prospective study of metabolic dysfunction in anti-psychotic-treated psychiatric patients from across the diagnostic spectrum, we investigated change in glycaemic status over time.

Materials and methods

We recruited 106 patients from psychiatric outpatient clinics in the Northeast of England between January 2002 and March 2004. Exclusion criteria and baseline characteristics of this cohort have previously been described (Mackin *et al.*, 2005). All patients were invited to participate in a follow-up study between June 2005 and December 2005. Subjects gave written informed consent to participate in this study, which was approved by the Newcastle Local Research Ethics Committee.

Participants were given written instructions to fast overnight on the day before assessment, and fasting status was confirmed on the

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morning of study by a member of the research team. All assessments were performed between 8.30 and 10.00 am on the study day. Venous blood was withdrawn for estimation of fasting blood glucose. We also gathered information from subjects and medical case-notes regarding any lifestyle intervention or referral to other healthcare professionals for management of metabolic disease (e.g., weight management, dietary advice, etc.) during the period between baseline and follow-up assessments. Impaired fasting glucose (IFG) was defined as fasting blood glucose between 6.1 and 7.0 mmol/L, and diabetes mellitus as fasting blood glucose >7.0 mmol/L (National Diabetes Data Group, 1979).

Results

Of the original 106 patients in the baseline cohort, 90 (85%) consented to participate in the current study. Mean duration between the baseline and follow-up visits was 599.3 days (SD ± 235.4; Range 328–1175). At follow-up mean age was 45.8 (SD ± 11.8) years; 49% were male; 98% were Caucasian. Diagnostic classification is as follows: bipolar disorder, 35.6%; schizophrenia, 30.0%; schizoaffective disorder, 10%; other, 24.4%.

Of the 90 patients prescribed anti-psychotic medication at baseline, 83 (92%) were still taking an anti-psychotic drug at follow-up. Sixty-eight (82%) patients were prescribed the same anti-psychotic regimen as at baseline assessment. Fifty-six (67.5%) were prescribed an atypical agent (olanzapine, $n = 35$, 42.2%; quetiapine, $n = 11$, 13.3%; risperidone, $n = 9$, 10.8%; clozapine, $n = 7$, 8.4%; and amisulpiride, $n = 3$, 3.6%); 18 (21.7%) patients were prescribed a typical agent (flupenthixol, $n = 8$, 9.6%; sulpiride, $n = 5$, 6.0%; chlorpromazine, $n = 4$, 4.8%; fluphenazine, $n = 2$, 2.4%; haloperidol, $n = 2$, 2.4%; trifluoperazine, $n = 2$, 2.4%; zuclopenthixol, $n = 2$, 2.4%; pipothiazine, $n = 1$, 1.2%); and 8 (9.6%) patients were prescribed a combination of a typical and an atypical agent. Twenty-two patients (26.5%) were prescribed anti-psychotic medication alone, and the remaining patients were co-prescribed other psychotropic medication including anti-depressants ($n = 48$, 57.8%), mood stabilizers ($n = 38$, 45.8%), benzodiazepines ($n = 23$, 27.7%) and anti-cholinergic drugs ($n = 15$, 18.1%).

During the follow-up period, 12 (13.3%) subjects changed glycaemic status and 78 (86.7%) remained unchanged (Figure 1). Of those subjects whose glycaemic status changed, 10 (83.3%) remained on the same anti-psychotic throughout the follow-up period. Blood glucose values and anti-psychotic drugs taken by these individual subjects are given in Table 1, together with details of any intervention during the follow-up period. Mean weight change in patients converting from normoglycaemia to IFG was +0.68 (SD ± 1.61) kg; mean weight change in patients converting from IFG to normoglycaemia was +0.78 (SD ± 0.71) kg.

Discussion

During a 19-moth follow-up period, 13% of patients changed glycaemic status. It is noteworthy that five out of six patients who were classified as having IFG at baseline had reverted to normoglycaemia at follow-up assessment; all five patients were taking a 'high-risk' drug (olanzapine = 4, clozapine = 1) at baseline, and all remained on the same drug at the same dose throughout the follow-up period. Also of interest is the observation that none of these patients received any lifestyle intervention to account for the change in glycaemic status.

IFG is associated with an increased risk of developing diabetes mellitus in the background population (Unwin *et al.*, 2002), and

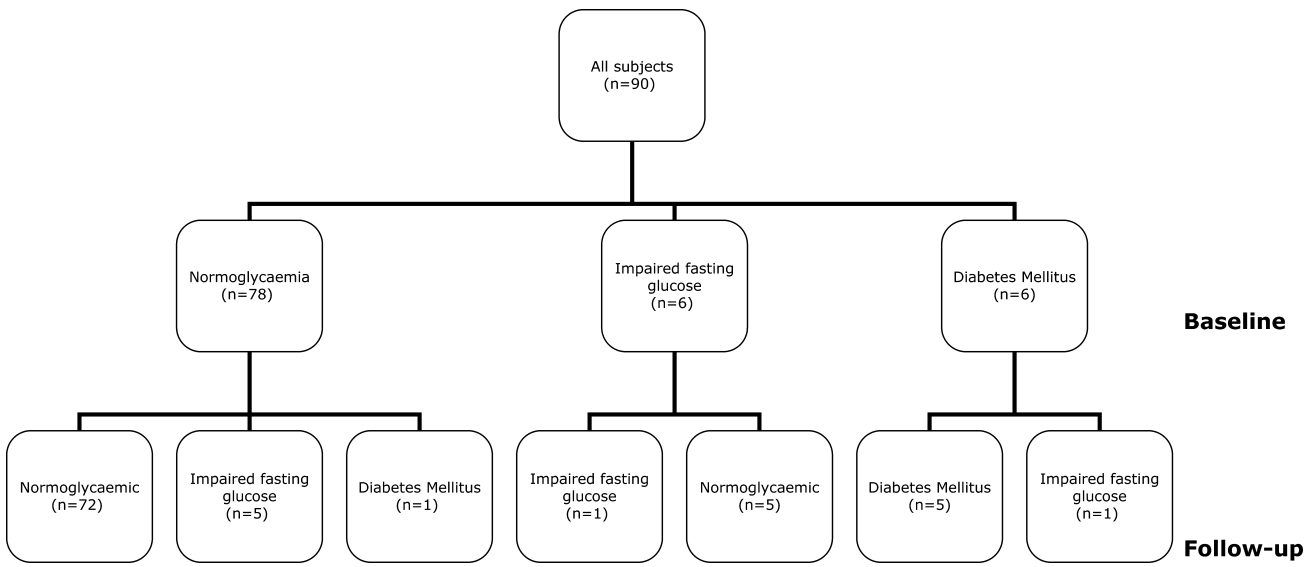

Figure 1 Glycaemic status of 90 patients at baseline assessment and follow-up.

Table 1 Anti-psychotic regimen, body mass index (BMI), fasting blood glucose and details of lifestyle intervention for 12 patients whose glycaemic status changed between baseline and follow-up assessments

	Anti-psychotic		BMI(kg/m^2)		FBG(mmol/L)		Lifestyle intervention
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	
Normoglycaemia → IFG							
1.	Quetiapine	Quetiapine	25.2	27.3	5.4	6.2	None
2.	Amisulpiride	Amisulpiride	25.5	26.8	5.1	6.4	None
3.	Sulpiride	Sulpiride	29.6	27.8	5.2	6.7	None
4.	Risperidone Zuclopenthixol	Rispseridone Zuclopenthixol	44.0	45.4	5.3	6.3	None
5.	Quetiapine	None	40.1	39.1	5.9	6.5	None
Normoglycaemia → DM							
1.	Olanzapine	Olanzapine	36.9	33.0	5.4	7.7	Practice Nurse
IFG → Normoglycaemia							
1.	Olanzapine	Olanzapine	31.2	31.2	6.1	5.7	None
2.	Olanzapine	Olanzapine	24.1	25.6	6.1	5.9	None
3.	Olanzapine	Olanzapine	29.7	30.2	6.9	5.4	None
4.	Clozapine	Clozapine	24.6	24.4	6.2	6.0	None
5.	Olanzapine	Olanzapine	27.0	28.5	7.0	5.5	None
DM → IFG							
1.	Flupenthixol Olanzapine	Flupenthixol Quetiapine	28.8	24.5	7.4	6.5	None

life style interventions, including weight loss and increased physical activity, are highly effective in preventing or delaying the onset of diabetes. It is not clear whether IFG in anti-psychotic-treated patients with mental illness has the same predictive value and evidence-based strategies for managing patients who develop IFG during anti-psychotic treatment are lacking.

Elevated fasting glucose is a result of raised hepatic glucose output and a defect in early insulin secretion. The mechanism(s) by, which anti-psychotic drugs influence glucose homeostasis are not well understood, but there is compelling evidence that some of the atypical agents cause significant weight increase (Consensus Development Conference, 2004), thus increasing the risk of glucose intolerance. Other mechanisms, independent of increasing adiposity, may also be important in the pathophysiology of anti-psychotic-induced glucose intolerance; the affinity of many atypical agents for serotonin or muscarinic receptors may underlie acute changes in glucose handling, but the longer term effects of serotonin and/or muscarinic antagonism on glucose homeostasis are not known.

The development of type 2 diabetes is closely related to increasing adiposity [assessed by increasing Body mass index (BMI)] (Colditz *et al.*, 1995), and the Finnish and American prevention of diabetes studies have shown the marked clinical benefits associated with weight reduction in terms of preventing the conversion to type 2 diabetes among high risk individuals with glucose intolerance (Lindström *et al.*, 2003; Tuomilehto *et al.*, 2001). Reversion from IFG to normoglycaemia in our cohort cannot be accounted for by reduced adiposity as only one patient in this group had a lower BMI at follow-up, the mean weight increase of the group being 0.78kg.

It is acknowledged that measurement error and biological variability can lead to different classification of an individual's glycaemic status when tested on more than one occasion (Unwin *et al.*, 2002). Two studies used fasting plasma glucose to define IFG, and then individuals were re-tested to determine the reproducibility of the test (Ko *et al.*, 1998; de Vegt, *et al.*, 2000). The kappa coefficients of these studies were 0.22 and 0.44 indicating fair to moderate reproducibility. The proportion of participants with IFG during the first study who were subsequently reclassified as having IFG during the re-test was 63.7% (Ko *et al.*, 1998) and 51.4% (de Vegt *et al.*, 2000).

Little is known about the natural history of abnormalities of glucose homeostasis in patients taking anti-psychotic drugs owing to a paucity of prospective studies investigating the evolution of glycaemic control in this population. One study, however, has reported improvement of glycaemic control in patients with established diabetes following anti-psychotic treatment. In a cohort of 157 patients with schizophrenia, Lindenmayer reported that four out of six patients with diabetes showed improved glucose tolerance following eight-weeks treatment with atypical anti-psychotics (olanzapine = 2, risperidone = 2) (Lindenmayer *et al.*, 2003). We are not aware of any other published studies that have investigated the natural history of IFG in anti-psychotic-treated patients.

Case reports and case series suggest that anti-psychotic treatment-related diabetes may be reversible following switching to a 'safer' agent (De Hert *et al.*, 2006; Peuskens *et al.*, 2004). A consensus statement from the USA also recommends switching to an alternative agent when patients develop worsening glycaemic control

during anti-psychotic treatment (Consensus Development Conference, 2004). Our findings suggest that progression from IFG to overt diabetes in patients treated with 'high-risk' drugs such as clozapine and olanzapine is not inevitable, even in the absence of lifestyle intervention. We would recommend caution in switching to another anti-psychotic drug simply on the basis of a change from normoglycaemia to IFG, especially if there is adequate symptomatic control of the mental disorder. Subjects developing IFG should undergo further investigation and ideally an oral glucose tolerance test to identify impaired glucose tolerance or undiagnosed diabetes. The monitoring of other cardiovascular risk factors such as adiposity and dyslipidaemias is also strongly recommended.

These findings, based on a relatively small sample size should stimulate further research on long-term changes in glycaemic control in patients treated with anti-psychotic drugs. In the absence of a sound evidence-base, decisions regarding the management of worsening glycaemic control in patients treated with anti-psychotic drugs are not straightforward. A careful risk-benefit analysis is needed in which control of the symptoms of the mental disorder is balanced against the potential for metabolic decompensation and increased cardiovascular risk.

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