Quetiapine-induced diabetes with metabolic acidosis

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Medication adherence with antipsychotics is adversely impacted by the burden of untoward adverse effects. In particular, sexual side-effects may interfere with compliance, but are often underreported by patients. Sexual dysfunction related to hyperprolactinemia is commonly described, but ejaculatory disturbance due to potent alpha1 adrenergic antagonism may also occur, and has been reported frequently with certain typical antipsychotics such as thioridazine, but rarely with atypical antipsychotics. Presented here is the case of a 51 year old male with schizophrenia who developed retrograde ejaculation on high dose risperidone therapy (8 mg/day) with prompt resolution of symptoms upon dose reduction. The absence of decreased libido or erectile dysfunction indicates that alpha1 adrenergic antagonism and not low serum testosterone due to hyperprolactinemia is the etiology for this side-effect. This case illustrates another mechanism for sexual adverse effects, and the need for routine inquiry into sexual dysfunction during atypical antipsychotic therapy. *Int Clin Psychopharmacol* 19:169–171 © 2004 Lippincott Williams & Wilkins.

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Introduction

There is increasing concern about the short- and long-term metabolic consequences of antipsychotic therapy in schizophrenic patients (Meyer, 2003). In part, this is traceable to such patients having twice the mortality rate from cardiovascular disease (CVD) as a group compared to the general population. Although smoking, hypertension and lipid abnormalities are recognized as traditional contributing risk factors for CVD, the third revision of the national cholesterol monitoring guidelines (ATP III) identified diabetes mellitus as being equivalent in risk for a major coronary event over 10 years to those diagnosed formally with coronary artery disease (Expert Panel on Detection and Adults, 2001).

Although US regulatory authorities are recommending labelling changes to suggest monitoring for hyperglycemia and diabetes in all patients on atypical antipsychotics, an abundance of data generated by biological and epidemiological studies over the past 5 years has generally indicated that clozapine and olanzapine are associated with higher risk for new-onset diabetes mellitus, glucose intolerance or diabetic ketoacidosis, whereas there are fewer studies implicating risperidone and ziprasidone with metabolic adverse effects (Gianfrancesco *et al.*, 2002; Jin *et al.*, 2002; Atmaca *et al.*, 2003; Cohen *et al.*, 2003; Gianfrancesco *et al.*, 2003; Koller *et al.*, 2003; Lindenmayer *et al.*, 2003; McIntyre, 2003; Taylor, 2003; Weiden *et al.*, 2003). Quetiapine is a dibenzothiazepine, which is structurally similar to the dibenzodiazepines olanzapine and clozapine and appears to share their propensity for induction of hypertriglyceridemia, but with a lesser degree of weight gain (Meyer, 2001a,b). Although the Japan Ministry of Health, Labour and Welfare, Safety Division, Pharmaceutical and Medical Safety Bureau has issued a warning regarding the use of quetiapine in patients with a history of diabetes, and required changes to the package insert, there is a paucity of data regarding the association between quetiapine and hyperglycemia or new onset diabetes mellitus, aside from a small number of case reports and retrospective case series (Sobel *et al.*, 1999; Domon and Cargile, 2002; Jin *et al.*, 2002; Sernyak *et al.*, 2002; Wirshing *et al.*, 2002; Sneed and Gonzalez, 2003; Wilson *et al.*, 2003), and one published large database study suggesting that quetiapine may also have a predilection towards induction of glucose intolerance (Sernyak *et al.*, 2002). Given this limited data, new cases where a strong causal association is indicated between the use of quetiapine and hyperglycemia help to reinforce the concept that this agent may possess similar metabolic risks as the structurally related compounds clozapine and olanzapine.

Case report

The patient was a 48-year-old, non-Hispanic, White male with a long-standing psychotic disorder variably

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Table 1 Patient treatment

Date	Weight (lb)	BMI (kg/m^2)	Serum glucose (mg/dl)	Comments
16 May 2001	162	22.03	101 (fasting)	Meds: Haloperidol 20 mg h.s.
16 October 2001	173.7	23.62	112 (fasting)	Meds: Haloperidol 20 mg h.s.
November 2002 to 5 March 2003 unmedicated				
5 March 2003 hospital admission	139	19.90	113 (fasting)	Meds: Quetiapine and haloperidol started, but refused until court petition approved 3/11/03
31 March 2003	147	19.99		Meds: Haloperidol 5 mg b.i.d. Quetiapine titrated to 400 mg b.i.d. by 3/24/03
5 April 2003	139.8	19.01		Meds: Haloperidol 5 mg b.i.d Quetiapine 400 mg b.i.d
9 April 2003			859 (random) Hb A_{1c} 12.1%	
14 June 2003	156	21.22	138 (fasting) Hb A_{1c} 7.3%	Meds: Risperidone 6 mg h.s. Lithium 1500 mg h.s. Metformin 500 mg a.m., 1000 mg h.s. (plus sliding scale insulin)

BMI, Body mass index; Hb A_{1c} glycosylated haemoglobin

diagnosed as schizophrenia or schizoaffective disorder bipolar type, with a history of poor medication adherence resulting in frequent hospitalization. This patient was quite delusional about his medications and insisted on taking haloperidol, although he achieved only modest therapeutic benefit. In 2001, during active treatment with haloperidol (Table 1) at an average dose of 20 mg/day, this patient gained nearly 12 lb and developed impaired fasting glucose (fasting glucose 112 mg/dl). He was admitted under court order on 31 October 2001 to a locked facility because of poor medication adherence resulting in repeated hospitalization, but was lost to follow-up late in November 2002 after discharge from the locked facility, and did not come to clinical attention until early March 2003 after being out of treatment and, by his own admission, homeless for several months. The patient was grossly psychotic on presentation to the hospital, had lost substantial weight (35 lb), and initially refused medication until a court petition for medication was granted on 11 March 2003. Despite the weight loss, there was evidence of impaired fasting glucose on admission laboratory evaluation (fasting glucose 113 mg/dl). In the hospital environment, the patient rapidly gained weight on the combination of haloperidol 5 mg b.i.d., and quetiapine, titrated to a dose of 400 mg bid, with an increase of 8 lb over the next 2 weeks. Despite good oral intake, the patient started losing weight and, by week 4, was back at his admission weight. Four days later, he was noted to be confused and lethargic, and laboratory investigation revealed a random glucose of 859 mg/dl, a glycosylated haemoglobin of 12.1%, and serum chemistries suggestive of metabolic acidosis (sodium 126, chloride 86). The patient was emergently admitted to the intensive care unit and treated with aggressive intravenous hydration and insulin. On his return to the psychiatric inpatient unit, the treatment team decided to discontinue quetiapine and haloperidol in favour of haloperidol monotherapy initially, and then over time opted for risperidone combined with lithium to help manage mood lability and other manic-like symptoms. Although the patient regained the weight lost during the period of presumed uncontrolled diabetes mellitus (31 March to 9 April 2003), the requirement for insulin rapidly diminished over the next 2 months. By the time of discharge in mid-June, the patient's glucose intolerance was primarily managed with an oral agent alone, metformin, with sliding-scale insulin used only to cover the patient's frequent dietary indiscretions.

Discussion

The reversibility, or improvement in, new-onset diabetes related to clozapine and olanzapine treatment has been noted in 78% of patients who are switched in to a less offending agent (Koller *et al.*, 2001; Koller and Doraiswamy, 2002; Wilson *et al.*, 2003), and the same appeared to be true in our present case where haloperidol and, later, risperidone were substituted for the quetiapine/haloperidol combination. Haloperidol is typically assumed to be a metabolically neutral medication, but our patient had already demonstrated a predilection towards glucose intolerance even when on that medication. The addition of high-dose quetiapine in our patient resulted in the rapid development of uncontrolled diabetes with metabolic acidosis, which, fortunately, occurred in a hospital setting where it was promptly treated.

The hospital course of our patient illustrates two important points regarding the development of diabetes mellitus associated with atypical antipsychotics. The patient's weight at the time his diabetes was diagnosed was identical to that at which time he entered treatment, a finding described in multiple cases (Jin *et al.*, 2002). However, in our patient, the availability of multiple weights demonstrates that he actually gained a significant amount of weight, and then abruptly began losing weight, most likely due to polyuria and catabolic effects from uncontrolled hyperglycemia. Thus, the development of rapid weight loss, perhaps more so than weight gain, is an important clinical clue that a patient may have developed

hyperglycemia and requires acute intervention. Second, despite regaining a substantial amount of weight on the risperidone and lithium combination beyond that experienced on quetiapine, his glycemic control continued to improve to the extent that routine insulin therapy was no longer required, thereby illustrating the concept that certain atypical agents may have a greater direct impact on glucose tolerance independent of the effects on weight gain. Cases such as this thereby reinforce the need for vigilance in monitoring of serum glucose during antipsychotic therapy, particularly when higher risk agents for hyperglycemia are employed, and the necessity of routine inquiry on each visit of the clinical signs of diabetes including excessive thirst, frequent urination, fatigue and unexplained weight loss.

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