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CASE REPORT

A patient treated with olanzapine developing diabetes de novo: proposal for hyperglycaemia screening

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ABSTRACT

We report a patient with schizophrenia who developed diabetes mellitus during treatment with olanzapine. The case confirms the pattern of atypical antipsychotic-related diabetic emergencies: rapid onset in relatively young patients, often with severe glucose derangements and serious complications. As diabetic emergencies have a high morbidity and mortality, regular glucose screening should be performed in patients with schizophrenia treated with atypical antipsychotics.

KEYWORDS

Atypical antipsychotics, diabetic ketoacidosis, hyperosmolar hyperglycaemic deterioration, olanzapine

INTRODUCTION

In the past decade, the prescription of the atypical antipsychotic drugs has been reported as a precipitating factor for diabetes mellitus (DM).[1] Diabetes in patients with schizophrenia treated with antipsychotics is usually classified as type 2 DM.[2] It is, however, often rapid in onset and presents as a syndrome with both characteristics of a hyperosmolar hyperglycaemic syndrome and diabetic ketoacidosis, with severe hyperglycaemia, hyperosmolarity, but also with ketoacidosis. We present a patient with schizophrenia, who developed DM *de novo* during treatment with the atypical antipsychotic drug olanzapine.

CASE REPORT

A 47-year-old male patient of African origin was brought into the emergency department of our hospital by ambulance because of a rapidly deteriorating level of consciousness, polydipsia and hypotension. The patient was referred from a psychiatric ward, where he had been treated for schizophrenia, paranoid type (DSM IV: 295.30), with olanzapine 15 mg/day for three months before admission.

On admission to the psychiatric ward three months earlier, the patient was violent and did not allow any invasive procedures. Olanzapine was started immediately. One month after his admission he agreed to blood glucose measurements. At that moment a nonfasting blood glucose was 9.6 mmol/l. Unfortunately, this elevated value did not reach the doctors' attention.

The patient had documented atopic rhinitis, for which he used a budesonide nose spray, and chronic bronchitis, for which he took a preventive dosage of doxycyline 100 mg/day and acetylcysteine 1200 mg/day.

Personal and family histories for diabetes mellitus were negative. Furthermore, he had no history of hypertension, dyslipidaemia, alcohol or drug abuse.

On physical examination he showed a decreased level of consciousness (EMV score 1-5-2), hypotension (RR 80/50 mm Hg) and decreased turgor. The patient's body mass index was 24.5 kg/m^2.

Laboratory analysis on admission (reference values between brackets) showed extreme hyperglycaemia of 118.7 mmol/l (<7.8), signs of severe dehydration (plasma creatinine 329 µmol/l (70-110)), serum sodium of 131 mmol/l (135-145), serum potassium of 4.3 mmol/l (3.5-5.0) and a slightly increased C-reactive protein of 19 mg/l (0-10). Blood gas

analysis showed metabolic acidosis: pH 7.07 (7.36-7.44), pCO_2 2.1 kPa (4.5-6.1), pO_2 12.7 kPa (10.0-14.0), HCO_3^- 4.5 (21-27), and anion gap 24 mmol/l (<12). Serum lactate was 2.25 mmol/l (0.63-2.43). Urine and blood cultures and chest X-ray showed no signs of infection. Unfortunately no urine analysis was performed for ketones.

The patient was admitted to the intensive care unit and treated with mechanical ventilatory support, with intravenous (iv) 0.65% sodium chloride, and iv insulin. During treatment he developed hypernatraemia and rhabdomyolysis (creatinine kinase 13410 U/l (0-200) on day 3).

After three days the patient could be detubated and after five days he could be transferred to the general ward where iv insulin was switched to subcutaneous (sc) insulin. Antipsychotic medication was switched from olanzapine to risperidone.

On hospital discharge he was using 28 units long-acting insulin combined with 16 units short-acting insulin three times a day. One month after discharge the insulin dose could be reduced to 16 units of long-acting insulin with 4 to 6 units short-acting insulin three times a day. Four months after discharge the sc insulin was replaced by metformin 1000 mg/day.

DISCUSSION

The patient described in this case report presented with severe life-threatening hyperosmolar hyperglycaemic deterioration of new-onset type 2 diabetes with characteristics of a ketoacidosis as well.

Such severe glucose disarrangements in such a short period in a patient who did not have documented diabetes mellitus, with a negative family history, without weight gain in the preceding period, and without the occurrence of other important precipitating factors for hyperosmolar deterioration such as infection, myocardial infarction, stroke, or excess alcohol consumption is very unusual for type 2 diabetes. After cessation of olanzapine, insulin dosages could be reduced rapidly, and the patient could eventually be started on oral antidiabetic agents.

The patient developed rhabdomyolysis. It was postulated that the hyperosmolar state inhibits the electrogenic sodium pump on muscle cells, impairing sodium-calcium transport, resulting in increased cytoplasmatic calcium levels which destroys muscle cells.[3]

Although several case reports describe the occurrence of diabetes mellitus with atypical antipsychotic use,[1] studies investigating relative risks of developing hyperglycaemia/DM in patients treated with olanzapine are not available. In a small study among 71 patients treated with olanzapine, 39% of these patients who did not have documented diabetes mellitus were hyperglycaemic (fasting plasma glucose >5.6 mmol/l).[4]

Several mechanisms have been proposed as to why olanzapine induces DM by influencing insulin secretion or insulin action. Firstly, olanzapine causes weight gain, thus increasing insulin resistance. However, as it has been shown that olanzapine can also induce diabetes without weight gain,[5,6] other mechanisms have to coexist. Both stimulating and inhibitory effects of atypical antipsychotics on insulin secretion have been mentioned.[7,8] The underlying molecular mechanisms are unknown. Clozapine, a related atypical antipsychotic, was found to inhibit insulin release through activation of K+ channels and thus hyperpolarisation of the cell membrane of pancreatic β-cells.[8] Suppression of compensatory insulin release has also been attributed to antagonism of muscarine receptors on the β-cells, as olanzapine is a potent nonselective muscarinic antagonist.[9]

Through similar mechanisms olanzapine might also act on cholinergic parasympathetic nerve endings to the liver, disrupting hepatic glucose metabolism.[9] In addition to these peripheral actions, certain atypical antipsychotics may affect central nervous system glucose regulation, either directly via the release of epinephrine and glucagon or via an effect on neural pathways to peripheral tissues.[9] Further research is necessary to unravel the molecular mechanism, as a better understanding of these mechanisms will influence the development of new agents without adverse metabolic effects.

Glucose monitoring is important in the prevention of hyperglycaemia/DM with antipsychotic treatment. A screening chart for hyperglycaemia in patients treated with atypical antipsychotics was proposed by the American Diabetes Association (*table 1*).[10] However, as glycaemic monitoring is considered impractical and costly,[11] it is often not practised. It has been shown that

Table 1. *Monitoring protocol for patients on atypical antipsychotics according to the American Diabetes Association (Diab Care 2004)*

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually
Personal history	X					X
Weight (BMI)	X	X	X	X	X	
Waist circumference	X					X
Blood pressure	X			X		X
Fasting plasma glucose	X	*	*	X	*	X

*Represent additional measurements as proposed by the authors for the first year of treatment with olanzapine.

most of the newly diagnosed diabetes cases developed within the first months after starting olanzapine treatment,[1] and therefore it seems logical to monitor more closely in this period. Patients with (multiple) risk factors for DM (African origin,[1] obesity, family history) should be checked even more closely.[12] Older age should not be regarded as a major risk factor, since it was found that a striking 75 to 91% of patients with schizophrenia during antipsychotic treatment developed diabetes before the age of 50 years.[13] We therefore advise monitoring glucose at monthly intervals in all patients, irrespective of age, during the most risky phase, i.e. the first three months of treatment with olanzapine. Then, quarterly monitoring is advised for the first year (*table 1*), after which we advise once yearly monitoring. Future research has to prove whether these monitoring intervals are strict enough to prevent diabetic emergencies.

As the various atypical antipsychotics differ in their potential for causing glucose dysregulation, with olanzapine having greater adverse effects on glucose levels than risperidone, quetiapine, and perfenazine, we advise switching to a one of these less adverse agents if disarrangements in glucose metabolism occur.[14] In our patient the insulin dose could soon be decreased by using risperidone and eventually the insulin was replaced by oral antidiabetic agents.

REFERENCES

1. Köller EA, Doraiswamy PM. Olanzapine-associated diabetes mellitus. Pharmacotherapy 2002;22:841-52.
2. Cohen D, Batstra MR, Gispen-de Wied CC. Immunological characteristics of DM in schizophrenia. Diabetologia 2005;48:1941-2.
3. Singhal PC, Abramovici M, Ayer S, Desroches L. Determinants of rhabdomyolysis in the diabetic state. Am J Nephrol 1991;11:447-50.
4. Sernyak MJ, Gulanski B, Rosenheck R. Undiagnosed hyperglycaemia in patients treated with atypical antipsychotics. J Clin Psychiatry 2005;66:1463-7.
5. Clark C, Burge MR. Diabetes Mellitus associated with atypical anti-psychotic medications. Diab Tech Ther 2003;5:669-83.
6. Ramankutty G. Olanzapine-induced destabilisation of diabetes in the absence of weight gain. Acta Psychiatr Scand 2002;105:235-7.
7. Melkersson K. Clozapine and olanzapine, but not conventional antipsychotics, increase insulin release in vitro. Eur Neuropsychopharmacology 2004;14:115-9.
8. Best L, Yates AP, Reynolds GP. Actions of antipsychotic drugs on pancreatic β-cell function: contrasting effects of clozapine and haloperidol. Psychopharm 2005; 19:597-601.
9. Housekecht KL, Robertson AS, Zavadoski W, Gibbs EM, Johnson DE, Rollema H. Acute effects of atypical antipsychotics on whole-body insulin resistance in rats: Implications for adverse metabolic effects. Neuropsychopharmacology 2007;32:289-97.
10. Diabetes Association. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diab Care 2002;27:596-601.
11. Cohn TA, Sernyak MJ. Metabolic monitoring for patients treated with antipsychotic medications. Can J Psychiatry 2006;51:492-501.
12. Newcomer JW. Medical risk factors in patents with bipolar disorder and schizophrenia. J Clin Psychiatry 2006;67 Suppl 9:25-30.
13. Cohen D, Dekker JJ, Peen J, Gispen-deWied. Prevalence of diabetes mellitus in chronic schizophrenic patients in relation to long-term antipsychotic treatment. Eur Neuropsychopharmacology 2006;16:187-94.
14. Lieberman JA, Scott Stroup T, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353:1209-23.