Hyperglycemia - induced by Olanzapine

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Olanzapine is an atypical antipsychotic (dopamine, serotonin antagonist) marketed in the US since 1996. It is preferred over older traditional (typical) antipsychotics because of its relatively low frequency of sedation, orthostatic hypotension, extrapyramidal symptoms and anticholinergic side effects. It is indicated for the management of schizophrenia, and short-term treatment of acute manic episodes in bipolar disorder.[1] In addition to approved indications, it has been administered for the treatment of psychosis in dementia and Parkinson's disease, delusional disorder or resistant depression, aggression and agitation in the elderly patients and delirium.[2] Known adverse reactions to Olanzapine include orthostatic hypotension, weight gain, akathisia, increased salivation and somnolence.[1] The relationship between diabetes, schizophrenia and antipsychotic drugs is complex and intriguing, as untreated patients with schizophrenia are known to suffer from diabetes more often than the overall population.[3] Published reports of hyperglycemia occurring in association with Olanzapine began in 1998. Many case reports, chart reviews, and some results from clinical drug trials implicate a relationship between hyperglycemia and treatment with Clozapine and Olanzapine in patients with schizophrenia, although a few cases of hyperglycemia have also been reported in patients taking Risperidone and Quetiapine.[4] There were 237 reported cases between January 1994 and May 2001 of new onset diabetes mellitus (80%) and exacerbation of preexistent diabetes mellitus (20%) after starting Olanzapine therapy. Approximately 73% of all cases of hyperglycemia appears within 6 months of starting Olanzapine therapy, 78% of patients had improved glycemic control when Olanzapine was discontinued or the dosage decreased. The range of Olanzapine dosage was 2.5-40 mg/day and the spectrum of reported illness ranged from mild glucose intolerance to diabetic ketoacidosis and nonketotic hyperosmolar coma and eventual death in 15 cases.[5]

We report a 44-year-old male Qatari patient who is known to have chronic paranoid schizophrenia, since January 1989. He is not known to have diabetes mellitus. He has a family history of diabetes, his mother and sister have Type 2 diabetes mellitus and his eldest brother has Type 1 diabetes mellitus. He is usually followed up as an outpatient at the Psychiatry Department of Hamad Medical Corporation, Doha, Qatar. He was admitted several times to the male psychiatric unit to control episodes of florid psychotic symptoms, mainly paranoid and somatic delusions. He was treated by different traditional antipsychotics. His paranoid delusion improved but the somatic one remained refractory to different classes of typical antipsychotic drug trials. Risperidone was started in August 2000 and stopped after 5 months, because his somatic delusion was still refractory to Risperidone 2 mg, 4 mg, and even 6 mg. During Risperidone drug trial, fasting blood glucose level was regularly checked with no change from its baseline (85 mg/dl). After one month (January 2001), he was still deluded, so he was switched from Risperidone to Olanzapine, starting with 10 mg tab/day, increased to 20 mg tab/day. An antidepressant, Fluvoxamine 100 mg tab was added to treat the depressive symptoms. Three months after starting Olanzapine, his blood glucose level showed mild fluctuation from its baseline, which was controlled at that time by diabetic diet alone. His somatic and paranoid delusion improved, and he was discharged to the outpatient clinic with continued monitoring of blood sugar. Nine months later, he was presented with dry mouth, polydipsia, polyurea and fatigue. His fasting blood sugar was 14.9 mmol/L (268 mg/dl) and increased within a few days to 35.1 (630 mg/dl). The patient was conscious, and with intact cognitive functions. He was directed to accident and emergency for urgent medical intervention. Laboratory investigations including liver, thyroid and kidney function tests were within normal range. Olanzapine was discontinued and he was kept on Fluvoxamine 100 mg tab. The elevated blood glucose showed resistance to insulin sliding scale and remained high for a few days. Oral hypoglycemic agent, Gliclazide 80 mg tab/bid was added to insulin coverage. Three days later, his blood glucose was still not controlled (19 mmol/L) and the Gliclazide dosage was increased to 100 mg tab/bid. Four days later Metformin 500 mg tab/bid was added to insulin sliding scale and Gliclazide tab. The fasting blood sugar level was decreased to 8 mmol/L within 3 days. Insulin sliding scale coverage was discontinued and Olanzapine was replaced by Risperidone 4 mg/day. After one month of follow-up, fasting and random blood sugar were still within normal range, Gliclazide and Metformin tab were stopped. Three months later diabetic diet was replaced with normal diet. Regular follow-up continued; first weekly, then bimonthly to monitor fasting and random blood sugar. The patient body weight was 100 kg at the start of Olanzapine drug therapy and increased to 102 kg when severe hyperglycemia developed. The last evaluation of the patient was carried out in August 2004. The patient

was still on regular diet; body weight decreased to 99 kg and remained normoglycemic.

In this case, Olanzapine appeared to increase the risk of acquiring type II diabetes. A rise in blood glucose can develop after a long time (9 months in this case), while most of the reported cases of hyperglycemia due to Olanzapine occur in the first 6 months.[5] Although there are some cases of hyperglycemia due to Risperidone use in the literature,[4] the patient in this study did not develop hyperglycemia during Risperidone drug trial of 5 months duration. The patient has a strong family history of diabetes mellitus and this could explain his susceptibility to develop hyperglycemia with Olanzapine drug treatment. So Olanzapine may be unmasking diabetes in genetically vulnerable patients. The postulated underlying mechanisms involved in this case and other reported cases of hyperglycemia due to Olanzapine are: 1. a decreased sensitivity to insulin that is independent of atypical medications, 2. an increased insulin resistance related to atypical medications, 3. the effect of atypical medications on serotonin receptors and, 4. overuse of insulin due to weight gain associated with drugs.[5] Some studies have attributed the weight gain as a risk factor in the development of hyperglycemia during the course of treatment with Olanzapine, but a few other studies decline this effect.[4] In this case, weight gain has no significant importance because the patient's weight just increased 2 kilograms during Olanzapine drug therapy. It seems that Olanzapine may cause hyperglycemia by a mechanism other than weight gain, and further research is needed to elucidate the mechanisms by which Olanzapine and other novel antipsychotics either cause diabetes or precipitate its onset. So close monitoring of blood glucose is necessary after initiation of Olanzapine to detect hyperglycemia. One of the major limitations in this report, the concomitant drug effect of Olanzapine and Fluvoxamine contributed to the hyperglycemia, which cannot be excluded.

In conclusion, Olanzapine can possibly increase the risk of acquiring type II diabetes, which is not dose dependent and is reversible. A family history of diabetes mellitus is considered as a risk factor. Florid hyperglycemia could not be explained in this case by the postulated weight gain as a risk factor. Routine monitoring of blood glucose level is necessary in patients receiving Olanzapine and, if hyperglycemia is observed, consider withdrawal of the drug to see if the condition remits.

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