Atypical neuroleptics and diabetes

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**SUMMARY**

Since a few years, an increasing number of cases of atypical neuroleptic-associated diabetes are reported in the literature. But few are dedicated to diabetologists. We report here two cases of patients with a severe deterioration of preexisting diabetes, with clozapine for the first case report and olanzapine for the second one. We also make a literature review and discuss the possible mechanisms involved in this atypical neuroleptic-associated diabetes. We recommend a thigh follow-up of weight, glycemic and lipidic parameters during psychotic patients treatment with atypical neuroleptics, in order to prevent or rapidly treat the metabolic complications described in the literature.

Mots-clés: Diabetes mellitus • Neuroleptics.

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**Résumé**

Neuroleptiques atypiques et diabète

Depuis quelques années, un nombre croissant de cas de diabète associé au traitement par neuroleptiques atypiques est observé dans la littérature. Mais seulement peu de ces cas sont adressés aux diabétologues. Nous rapportons ici, deux cas de patients ayant eu une sévère aggravation de leur diabète suite à un traitement par clozapine pour le premier patient, et suite à un traitement par olanzapine pour le second. Nous avons également réalisé une revue de la littérature et discuté des possibles mécanismes impliqués dans l’association neuroleptiques atypiques et diabète. Nous recommandons un suivi rapproché du poids, ainsi que des paramètres glycémiques et lipidiques, chez les patients psychotiques traités par neuroleptiques atypiques. Un tel suivi est indispensable pour prévenir et traiter rapidement les complications métaboliques décrites dans la littérature.

Mots-clés: Diabète • Neuroleptiques.

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Atypical neuroleptics are members of a new class of neuroleptics called dibenzodiazepines. Since the first introduction in US in 1989, they are largely used in schizophrenia and others psychosis treatment. They induce less extrapyramidal effects and hyperprolactinemia than conventional neuroleptics. However, some others secondary effects have been described, like agranulocytosis, sedation, constipation, hypersalivation and weight gain. Atypical neuroleptics are antagonists of central dopaminergic receptors, with specific effects: a high affinity for D3 and D4 receptors and a weak affinity for D2 receptors. As D2 receptor is expressed in limbic system, striatum, hypophysis, as in adrenal gland [1], conventional neuroleptics which strongly block it, induce extrapyramidal effects and hyperprolactinemia. D3 receptor, for the most part of it, is restricted to limbic system. D4 receptor is expressed on retina, prefrontal cortex, hypothalamus and also glomerular zone [2]. Atypical neuroleptics also strongly antagonize serotoninergic receptor 5HT-2 and some authors have suggested that their interaction with specific serotonin receptors may results in metabolic abnormalities like hyperglycemia [3]. This neuroleptics also produces a potent blockade of central adrenergic, histaminergic (H1) and muscarinic receptors.

Since the first case report of a diabetic ketoacidosis with clozapine in 1994 [4], a lot of atypical neuroleptic-associated diabetes cases have been reported. These represented either acute situations with ketoacidosis [5-7], de novo onset diabetes mellitus [8-10] or marked deterioration of glycemic control in a preexisting diabetes [8, 11]. Two molecules resumed most of case reports of diabetes with atypical neuroleptics: clozapine and olanzapine. Surprisingly, case reports are mainly published in the psychiatric literature, and only a few are dedicated to diabetologists.

**Case reports**

We report here two cases of worsening preexisting diabetes in two psychotic patients treated with such atypical neuroleptics.

**Mr D**, 59-year-old, was admitted to the hospital in 2000 for a severe hyperglycemia, 3 months after starting clozapine. He had a type 2 diabetes mellitus since 1996; his body mass index was 30 kg/m². He was treated by a sulfonylurea therapy, because of a metformine intolerance. He had normal glucose indices with HbA₁c between 7 and 7.5% before institution of clozapine therapy. The patient started clozapine daily, to control repeated psychotic episodes refractory to treatment with conventional neuroleptics. Three months later, he was admitted for asthenia and polyuropolydipsia. The laboratory data showed severe hyperglycemia at 30 mmol/l, with urinary ketones and without acidosis. HbA₁c was of 13.4%. The patient has received intravenous insulin and 5% dextrose fluid. One week later, the olanzapine was discontinued. He remained metabolically stable with the same regimen of insulin he had before starting olanzapine. The probably bad therapeutic observance and the olanzapine treatment are two events susceptible to explain the severe hyperglycemia in this patient. The short time between the olanzapine starting and the severe hyperglycemia with ketone bodies (15 days), and the rapidly improvement of the glycemic indices after the olanzapine regimen was discontinued are both worthy to note.

**Mr A**, 16-year-old, was admitted in the hospital in 2002, for a severe hyperglycemia, 15 days after starting olanzapine. He had a type 1 diabetes since he was 4 years. He was usually treated by 2 insulin injections daily. The patient started olanzapine daily (20 mg/j), to control repeated psychotic episodes refractory to treatment with conventional neuroleptics. Fifteen days later, he was admitted for asthenia, polyuria and weight loss (1 Kg). The laboratory data showed severe hyperglycemia at 30 mmol/l, with urinary ketones and without acidosis. HbA₁c was of 13.4%. The patient has received intravenous insulin and 5% dextrose fluid. One week later, the olanzapine was discontinued. He remained metabolically stable with the same regimen of insulin he had before starting olanzapine. The probably bad therapeutic observance and the olanzapine treatment are two events susceptible to explain the severe hyperglycemia in this patient. The short time between the olanzapine starting and the severe hyperglycemia with ketone bodies (15 days), and the rapidly improvement of the glycemic indices after the olanzapine regimen was discontinued are both worthy to note.

**Discussion**

The spectrum of reported diabetes mellitus associated with atypical neuroleptics is large. It ranges from mild glucose intolerance to diabetic ketoacidosis and non ketonic hyperosmolar coma. A recent epidemiologic descriptive study [12] identified 384 case reports of hyperglycemia occurring in clozapine-treated patients in the last 11 years. Of these reports, 54 published cases concerned an exacerbation of preexisting diabetes. Furthermore, it seems evident that several cases of worsening diabetes with atypical neuroleptics are not published and so are unregistered. An other large epidemiologic study, collected the data of 2.5 millions clozapine-treated patients in USA [13] and corroborate the association between clozapine (odds ratio = 7.44), olanzapine (odds ratio = 3.10), and even some of conventionals neuroleptics, and diabetes.

A five-year prospective study [14] have shown an increased incidence of diabetes in the clozapine treated patients. Thirty of the 82 patients (36.6%) were diagnosed with diabetes during the five-year follow-up. Of these diabetic patients, 11 were treated by diet alone, 14 were treated by oral hypoglycemic agents, 4 were treated by insulin, and one of them had a ketoacidosis. But this study is opened to criticism because of the absence of comparison group with patients treated with conventional neuroleptics. The only randomized double-link study [5] was realized on 101 patients treated with typical or atypical neuroleptics studied during...
14 weeks. The authors show a significant increased in glycemic levels for 74% of the clozapine and olanzapine treated patients (but with haloperidol and risperidone too), with a diabetes diagnostic for 15% of the patients. The risperidone statute is controverted. The most part of studies [13, 28] demonstrated an absence of relation between risperidone and diabetes.

In the literature, the relative risk to develop a clozapine or olanzapine associated diabetes-mellitus is clear and the incidence ranges from 15% to 35%. More of the increasing number of case reports, there are other arguments for an association between atypical neuroleptics and diabetes: the temporal relation to clozapine or olanzapine initiation, the prompt reversibility on withdrawal of the drug in several patients, and particularly the reintroduction tests. Koller [12] reports effectively a rapid onset of diabetes: in 27% of patients, diabetes was diagnosed within the first month of clozapine therapy, and in 56%, within the first 3 months. The most surprising cases are the ketoacidosis, without diagnostic of preexisting diabetes, reversible on withdrawal of the drug [6, 7, 14-17] and the positive reintroduction tests [6]. But the ketoacidosis accidents incidence is still unknown.

It is particularly difficult to conclude a link between atypical neuroleptics and diabetes. Indeed, the schizophrenic patients have a increased prevalence of type 2 diabetes even without neuroleptic treatment [10, 14, 18]. The exact reasons are unclear, but such factors as life style, diet rich in fats and carbohydrates, and lack of exercise may contribute to its development [19]. Increased amounts of visceral fat in drug-free schizophrenic patients have also been found, using CT scanning [20].

The mechanisms which could mediated a clozapine-induced glucose metabolism alteration are not known. First, there are some arguments for an increased insulin resistance with clozapine and olanzapine. Several studies have reported a significant weight gain with atypical neuroleptics [21]. But, surprisingly, there is no correlation between occurrence of diabetes and weight gain [10, 14, 18]. Furthermore, the prompt onset of diabetes in many patients strongly argues against a primary role for weight gain, although it may contribute to the late-onset hyperglycemia that was observed. On the other hand, clozapine has recently been linked to hypertriglyceridemia [14, 23] and to an increased amount of leptine [24]. But further investigation are necessary to elucidate if the hypertriglyceridemia and the increased amount of leptine are linked to the weight gain or not. Another potential factor of insulin resistance is the lack of physical activity, because of the sedating quality of atypical neuroleptics. Furthermore, by measuring the HOMA-R (homeostasis model insulin resistance) in a patient with ketoadicosis with clozapine, Collin suggest an increased insulin resistance as the underlying mechanism [6]. It may be supported by the observation of a clozapine-dependent decrease of glucose transport in muscular cells, due to the inhibition of the Glu4 transporter [25].

Avram demonstrated an insulin resistance by an euglycemic clamp study, associated to a reduction in β-cell function using intravenous glucose tolerance testing (IVGTT) when the oral glucose tolerance testing return to normal [17]. This tests were realized 60 and 320 days after a clozapine-induced ketoacidosis, in favor of a preexisting defect in insulin secretion and insulin action in this patient. But the cases reported of diabetes with atypical neuroleptics have not a higher prevalence of diabetes family history than the other schizophrenic patients.

Pollmacher [26] describe an increased amount of TNFα in the plasma of patients treated by clozapine. It is very interesting because we can also hypothesis an inhibition of the signaling events downstream the insulin receptor, by the TNFα released by clozapine. But this increased of TNFα with clozapine must be confirmed, because of discordant observations [27].

On the other hand, the acute ketoacidosis described with olanzapine and clozapine are consistent with a defect in the insulin secretion. Gatta [7] found a basal C-peptide decreased and a very poor response to glucagon, in a patient with ketoacidosis with olanzapine. But the mechanisms by which the insulin secretion can be altered are not yet elucidated. We can hypothesis a direct toxicity of olanzapine and clozapine on the pancreatic β cells, but there is no overt chemical similarity between this molecules and known islet cells toxins, such as alloxan, pentamidine, and streptozocin. Further studies in vitro are needed to test this hypothesis.

The antiislet-cell antibodies, the antiglutamic acid decarboxylase antibodies and the human insulin antibodies were founded negative in two cases [7, 17]. But, unfortunately, this antibodies are rarely analyzed. Interestingly, a lot of published case reports of clozapine or olanzapine-associated diabetes involved African American patients [4, 8, 9, 11, 14, 15]. This data suggest that the clozapine or olanzapine-associated diabetes could be related to the type 1 non-autoimmune diabetes, in some respects.

This review of the literature strongly suggests that there is a causal relationship between clozapine and olanzapine and either development or worsening of diabetes. With the extended use of this atypical neuroleptics, clinicians should be alerted of this potential complication. Further studies will be needed to define precisely the risk factors for diabetes in patients treated with clozapine or olanzapine.

Conclusion

One can conclude that there are enough arguments to recommend a tight follow-up of weight, glycemic and lipiddic parameters during psychotic patients treatment with atypical neuroleptics, in order to prevent or rapidly treat these metabolic complications.
References


