CASE REPORT

Diabetic ketoacidosis and severe hypertriglyceridaemia as a consequence of an atypical antipsychotic agent

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SUMMARY
The atypical antipsychotic agent clozapine, although an effective treatment for schizophrenia, is linked with metabolic adverse effects. We report a case of diabetic ketoacidosis and very severe hypertriglyceridaemia associated with clozapine use, in a patient with type 2 diabetes mellitus, who was successfully treated with continuous insulin infusion and fluids. As clozapine proved to be the most efficacious in controlling the patient’s psychotic symptoms, the patient has been continued on clozapine despite its known metabolic side effects. Importantly the patient has achieved satisfactory long-term lipid and glycaemic control. The current recommendations related to the metabolic care for patients treated with atypical antipsychotic agents as well as the mechanisms behind abnormal glucose and lipid regulation with clozapine therapy are discussed.

BACKGROUND
Atypical antipsychotic medications (clozapine, risperidone, olanzapine, amisulpride, aripiprazole and quetiapine) cause less extrapyramidal side effects than conventional agents.1 Owing to this advantage they are used as a first-line treatment for a variety of psychiatric disorders. Atypical antipsychotics are frequently associated with adverse metabolic side effects including new onset of diabetes mellitus, worsening control of existing diabetes mellitus and abnormalities in lipid metabolism.2–4 There are limited reports linking atypical antipsychotics with diabetic ketoacidosis (DKA) in patients with type 2 diabetes mellitus and with very severe hypertriglyceridaemia (serum triglycerides >22 mmol/L).5 We report a case of DKA and very severe hypertriglyceridaemia which was associated with chronic clozapine use, successfully treated with continuous insulin infusion. The present case adds to the literature linking atypical antipsychotic agents with severe metabolic abnormalities.

CASE PRESENTATION
A 44-year-old man with stable schizoaffective disorder on clozapine treatment, prescribed by an outpatient psychiatric service, presented with abdominal pain, vomiting and a 1 month history of polyuria and polydipsia. He was diagnosed with type 2 diabetes mellitus, 5 years prior to the current presentation. As the patient declined the proposed lifestyle and pharmacological intervention for his diabetes, his diabetes control was poor with documented glycosylated haemoglobin (HbA1c) of 12.0% 2 years earlier. He also had raised, untreated triglyceride level of 3.7 mmol/L (reference range (RR) <2.0 mmol/L). The patient had a positive family history for diabetes mellitus with his mother being affected.

The patient was diagnosed with schizoaffective disorder at the age of 28. His initial treatment was complicated by extrapyramidal side effects from conventional medications and mood stabilisers. Despite trials of concurrent olanzapine, lithium and valproate therapy the patient continued to experience positive psychotic symptoms including persecutory delusions, irritability and auditory hallucinations. Therefore, he was started on clozapine, 3 years after the diagnosis of his schizoaffective disorder. Following the initiation of clozapine the patient’s mental state stabilised without relapses requiring hospitalisation. Clozapine use for his schizoaffective disorder preceded the diagnosis of diabetes mellitus by ~8 years. The patient regularly collected prescriptions for his clozapine and his adherence to treatment was monitored by measurement of serum clozapine levels, which were within therapeutic range. As clozapine is associated with serious blood dyscrasias the patient was undergoing regular full blood count testing. However, the patient declined periodical assessments of his metabolic risk factors through the psychiatric clinic opting instead to monitor his diabetes control through his general practitioner, which he failed to do.

On examination, the patient had a normal body mass index (BMI) of 22.4 kg/m² and no evidence of hepatosplenomegaly, eruptive xanthoma or peripheral neuropathy.

INVESTIGATIONS
On presentation his biochemistry results revealed metabolic acidosis with pH 7.15 and HCO3 of 19 mmol/L, blood sugar level (BSL) of 23.3 mmol/L, the presence of urinary ketones (RR>160 mg/dL) and lactate of 2.1 mmol/L. The patient also had hyponatraemia with sodium of 126 mmol/L, an elevated urea of 7.4 mmol/L (RR 2.9–7.1) with normal potassium (4.9 mmol/L) and creatinine (78 μmol/L). Severe dyslipidaemia was identified with total cholesterol of 16.7 mmol/L (RR 3.0–5.5 mmol/L), low-density lipoprotein (LDL) cholesterol of 6.4 mmol/L (RR<2.5 mmol/L), high-density lipoprotein cholesterol of 1.1 mmol/L (RR 0.7–1.1 mmol/L) and a very severe hypertriglyceridaemia (triglyceride levels of 56.4 mmol/L, RR<2.0 mmol/L). Lipase, amylase and white cell count were normal. There

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was no evidence of thyroid dysfunction, Cushing syndrome or nephrotic syndrome. He had negative autoimmune antibodies (antiglutameric acid decarboxylase) and antibodies against tyrosine phosphatase-like protein and measurable, although low, C peptide of 0.08 nmol/L, supportive of the diagnosis of type 2 diabetes. His HbA1c was 14.6%.

**TREATMENT**

The patient was diagnosed with DKA and treated in the high dependency unit with insulin infusion, intravenous rehydration, electrolyte replacement and deep venous thrombosis prophylaxis. The acidosis was corrected within 16 hours of insulin infusion, initially started at the rate of 3 units of insulin per hour. The triglycerides decreased from 56.4 to 36.3 mmol/L within 9 hours of insulin infusion. After 32 hours of continuous insulin infusion, the patient’s triglycerides further decreased to 20.8 mmol/L. The insulin infusion was continued for 92 hours (329 units of insulin in total) and it was discontinued when the triglycerides reached 10 mmol/L. He was then started on a subcutaneous insulin basal–bolus regime as well as on fenofibrate and rosvastatin.

Clozapine was withheld at the beginning of the hospital admission and replaced with amisulpride. Stopping clozapine led to deterioration in the patient’s mental state with delusions and hallucinations. Therefore, in consultation with the psychiatric service, clozapine was reintroduced as trials of other antipsychotics in the past proved to be ineffective in controlling his schizoaffective disorder. The clozapine dose was gradually increased to 150 mg per day with a notable improvement in the patient’s mental state. The patient’s final diabetes mellitus treatment regime consisted of saxagliptin 5 mg daily, metformin extended release 1000 mg a day, insulin glargine 52 units daily and insulin aspart 18 units with breakfast, 22 units with lunch and dinner.

**OUTCOME AND FOLLOW-UP**

The lipid profile normalised prior to discharge from the hospital while on fenofibrate 145 mg daily and rosvastatin 20 mg daily with total cholesterol of 3.5 mmol/L, LDL cholesterol of 2.0 mmol/L and triglycerides of 1.9 mmol/L. The patient’s lipid profile has remained well controlled with total cholesterol of 3.4 mmol/L and triglycerides of 1.6 mmol/L, on the same doses of lipid-lowering agents, 12 months postinital presentation (table 1 and figure 1). As the patient has complied with his treatment regime, his diabetes control has remained adequate with the recent HbA1c of 7.6%. The patient continues on clozapine treatment with marked improvement in his mental state.

**DISCUSSION**

Mental illness is associated with an increased prevalence of diabetes with an approximately twofold to threefold increase in cardiovascular mortality.8 Although clozapine treatment is particularly effective for individuals with treatment-resistant schizophrenia data from primary observational and retrospective studies indicate that this medication is associated with adverse metabolic effects3 4 8 9 and increased premature death due to fatal cardiovascular events.10 The exact mechanism by which clozapine can affect glucose regulation is unknown; however, substantial evidence indicates that clozapine use is associated with the greatest propensity for weight gain among the antipsychotic agents and dose-dependent insulin resistance.11 Clozapine has been shown to inhibit glucose uptake via interaction with glucose transporter proteins receptors with a toxic effect on pancreatic cells.12 Other studies however point to reductions in insulin sensitivity in patients with diabetes through adiposity-independent mechanisms including increased leptin level and through the antagonism of dopamine, histaminic and serotonin 5-HT2c and 5-HT1A receptors.13

In some reports, clozapine use has also been linked with severe metabolic abnormalities including the rapid onset of DKA in younger people with type 2 diabetes.14 The mechanism behind such association is unclear and while not fully defined, is thought to be independent of weight gain and insulin resistance, possibly resulting from the direct effect of clozapine on β-cell function with suppressed insulin secretion.15

We report a case of DKA and very severe hypertriglyceridaemia which was associated with chronic clozapine use, successfully treated with continuous insulin infusion. As clozapine proved to be the most efficacious in controlling the patient’s psychotic symptoms, the patient has been asked to continue on this medication despite its known metabolic side effects. Importantly, the patient has adhered to his prescribed medical regime and he has achieved satisfactory lipid and glycaemic control.

Our case contributes to the expanding literature linking second generation atypical antipsychotic agents, in particular clozapine, with severe metabolic abnormalities including a new DKA in patients with negative autoimmune diabetes. DKA in our patient occurred 5 years after the diagnosis of poorly controlled diabetes, most likely triggered by the prolonged glucotoxicity towards the pancreatic cells. The patient did not experience significant weight gain while on clozapine treatment suggesting other than adiposity clozapine’s effect on glucose metabolism. Clinical studies have demonstrated that clozapine can impair glucose regulation and cause significant insulin resistance in the absence of weight gain or obesity.16 Houseknect et al16 showed that even following a single dose, there was severe and acute insulin resistance in mice, which was most

**Table 1** Metabolic indices and laboratory parameters during clozapine use

<table>
<thead>
<tr>
<th>Dates</th>
<th>2 years prior HA</th>
<th>Day 1 (HA)</th>
<th>Day 10 (HA)</th>
<th>Follow-up 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>12.0%</td>
<td>14.6%</td>
<td>NA</td>
<td>7.6%</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>3.7</td>
<td>56.4</td>
<td>1.9</td>
<td>1.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22</td>
<td>22.4</td>
<td>22.4</td>
<td>27</td>
</tr>
<tr>
<td>Diabetes treatment</td>
<td>Nil</td>
<td>Nil</td>
<td>Saxagliptin, metformin, insulin</td>
<td>Saxagliptin, metformin, insulin</td>
</tr>
<tr>
<td>Lipid treatment</td>
<td>Nil</td>
<td>Nil</td>
<td>Rosuvastatin, fenofibrate</td>
<td>Rosuvastatin, fenofibrate</td>
</tr>
<tr>
<td>Clozapine use (Y/N)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Other antipsychotics (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

HA, hospital admission; NA, not applicable. BMI, body mass index; HbA1c, glycosylated haemoglobin; N, no; Y, yes.

**Figure 1** Changes in triglyceride levels over time. HA, hospital admission.
likely due to hepatic insulin resistance. Hyperglycaemia and insulin resistance may also be mediated by the release of endorphins and activation of the hypothalamic cholinergic pathway which increases glucagon secretion.16

The interesting aspect of this case is the severe hypertriglyceridaemia. Despite its unique severity, there was no evidence of serious complications such as acute pancreatitis and hyperviscosity syndrome. Although severe hypertriglyceridaemia is a recognised feature of type 2 diabetes and a very uncommon consequence of DKA, atypical antipsychotic agents have also been reported to induce hypertriglyceridaemia through their effect on body weight and adiposity.17 Weight gain and increased resistance of hepatic transcription factor FoxO1 and adipose tissue lipoprotein lipase to the circulating insulin led to an increased lipogenesis with overproduction of very low-density lipoprotein and increase in free fatty acids (triglycerides and glycerol).18 In the present case extreme dyslipidaemia occurred in the absence of weight gain raising the possibility of a direct effect of clozapine on lipid metabolism.

Evidence for the use of insulin infusions to treat severe hypertriglyceridaemia is limited. Henderson et al19 examined the use of continuous insulin infusion for the treatment of severe hypertriglyceridaemia (triglycerides >15 mmol/L) in 15 patients with type 2 diabetes mellitus (new or established). Insulin infusion was continued for 48–72 hours and it effectively resulted in a significant reduction in severe hypertriglyceridaemia in all the examined patients.19 The researchers concluded that the use of insulin infusion was a safe treatment for the rapid correction of severe hypertriglyceridaemia.19 Intravenous insulin decreases triglycerides by enhancing lipoprotein lipase activity which converts triglycerides into fatty acids and glycerol. It may also reverse selective hepatic insulin resistance most likely through the decreased production of transcription factor SREBP-1c which is responsible for the synthesis of cholesterol and fatty acids in cells.20

Psychiatrists and primary care physicians should be familiar with the metabolic complications associated with the use of atypical antipsychotic agents. Prior to initiation of atypical antipsychotic agents such as clozapine and olanzapine patients should have their baseline weight and BMI recorded with compulsory screening for the presence of diabetes mellitus and lipid abnormalities. The American Diabetes Association/American Psychiatric Association published statement21 recommended weight monitoring at 4, 8 and 12 weeks after initiating therapy with new antipsychotic agents followed by quarterly routine visits to measure plasma glucose and lipids. This should be followed by annual monitoring of fasting plasma glucose or HbA1c with lipid monitoring to occur at least every 5 years.21

Further research is required to understand the relationship between newer antipsychotic medications such as clozapine and glucose and lipid metabolism. An improved understanding of the mechanisms behind the metabolic side effects of these medications could prevent the development of cardiovascular disease, stroke and death in the vulnerable group of patients with treatment-resistant schizophrenia or schizoaffective disorder.

**Contributors** KH and MMB wrote the draft of the manuscript. KH was involved in the revision of the manuscript. MMB revised the manuscript critically for important intellectual content and she approved its final version prior to the submission of this manuscript for publication.

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**REFERENCES**
