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B Cooper and others

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Olanzapine-induced multifactorial chylomicronaemia syndrome: a rare but important complication

Bridget Cooper, **Kenrick Blaker** and **Jerry R Greenfield**

St Vincent's Hospital, Garvan Institute of Medical Research, St Vincent's Hospital, University of New South Wales, Australia

Correspondence should be addressed to B Cooper
Email
bacooper311@gmail.com

Summary

We present a case of a 42-year-old man who developed acute onset severe hypertriglyceridaemia within days of commencing olanzapine therapy. Despite having a family history of metabolic syndrome, he had no personal history of hyperlipidaemia and had normal fasting lipids 1 week prior to treatment initiation. His case is consistent with a diagnosis of multifactorial chylomicronaemia syndrome with a possible undiagnosed underlying genetic lipid metabolism disorder. Our case highlights the difficulty in identifying patients at risk of severe hypertriglyceridaemia prior to the commencement of olanzapine.

Learning points

- Atypical antipsychotic medications, in particular olanzapine and clozapine, are associated with metabolic side effects.
- Olanzapine can precipitate acute onset severe hypertriglyceridaemia consistent with multifactorial chylomicronaemia syndrome.
- It is difficult to predict individuals at risk of olanzapine-induced hypertriglyceridaemia.
- This case demonstrates the importance of metabolic screening prior to the commencement of olanzapine and the possibility of repeating fasting serum lipids soon thereafter.

Background

Antipsychotics are often the mainstay of treatment for schizophrenia, but many are associated with metabolic side effects such as weight gain, lipid disturbance and glucose dysregulation. The prevalence of obesity, type 2 diabetes and hypercholesterolaemia in people with schizophrenia is estimated to be 3–5 times higher than in the general population (1). Therefore an additional increase caused by antipsychotic medications is likely to increase metabolic complications further. In a meta-analysis of 18 different antipsychotics, olanzapine was found to have the most marked effect on body mass index and LDL cholesterol, with statistically significant impacts on body weight, total cholesterol and triglyceride levels (1).

In recent years, there have been reports of severe hypertriglyceridaemia with olanzapine use in the absence of other metabolic complications, such as substantial weight gain or hyperglycaemia (2). Olanzapine has also been implicated in multifactorial chylomicronaemia syndrome (MFCS), a condition characterised by acute onset severe hypertriglyceridaemia in a genetically susceptible individual (3). Though there have been several studies suggesting that hypertriglycaemia occurs within 2–3 weeks of treatment initiation (2), to our knowledge

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this is the first case reported case of severe acute onset hypertriglyceridaemia in Australia.

Case presentation

A 42-year-old man presented to the emergency department at a major tertiary referral hospital with severe generalised pain. He described sudden onset of back, abdominal and limb pain upon waking that morning. He had no other symptoms, particularly gastrointestinal. Ten days earlier, he had been discharged from the hospital after a short admission for methamphetamine-induced psychosis, where he had been commenced on olanzapine 5 mg twice a day. Prior to its commencement, his metabolic screen was normal with fasting serum cholesterol of 3.6 mmol/L, fasting triglyceride of 0.6 mmol/L, fasting blood glucose level of 4.9 mmol/L and glycosylated haemoglobin (HbA1c) of 33 mmol/mol (5.2%). Unfortunately, a pre-treatment weight was not recorded. His past medical history was significant for borderline personality disorder, methamphetamine dependence and previous alcohol dependence. He had a family history of diabetes mellitus and coronary artery disease. He denied significant alcohol intake in the days prior to his current admission.

On examination, he was haemodynamically stable but febrile to 38.3°C. His weight was 73 kg with a calculated body mass index of 23.6 kg/m^2. His abdomen was soft and non-tender. The rest of his examination was unremarkable including a normal electrocardiogram.

Investigations

Investigations revealed a mild transaminitis, with alanine transaminase (ALT): 134 U/L (0–40), aspartate transaminase (AST): 104 U/L (0–35), alkaline phosphatase (ALP): 119 U/L (30–110), with a normal gamma glutamyl transferase (GGT) and bilirubin. He had a mildly elevated serum lipase of 72 U/L (0–60) and a normal serum amylase. A CT of his abdomen, pelvis and lumbosacral spine did not identify a cause for his symptoms. A septic screen was also unremarkable. Further investigations revealed fasting hypercholesterolaemia, with a serum cholesterol of 8.7 mmol/L, severe hypertriglyceridaemia, with a serum triglyceride level of 32.6 mmol/L and a serum blood glucose level of 6.4 mmol/L.

Treatment

Our patient was initially managed with nil oral intake and commenced on an insulin and dextrose infusion at 3 units per hour with 10% glucose via variable rate with regular serum lipid monitoring. His olanzapine was ceased. Over the next 24 h, his symptoms improved and serial serum lipids revealed a rapid improvement in hypertriglyceridaemia to 3.4 mmol/L.

Outcome and follow-up

Within 24 h of presentation, our patient's triglycerides were significantly improved and the insulin and dextrose infusion was ceased. He was transitioned to fenofibrate 145 mg nocte and rosuvastatin 20 mg nocte with the commencement of oral intake. Within 48 h, he was discharged home with repeat serum lipids revealing normalised serum cholesterol and triglyceride levels.

Discussion

Many atypical antipsychotics are known to cause weight gain and increased development of metabolic syndrome in patients. Olanzapine and clozapine have been identified as having the greatest effect on weight gain and hypercholesterolaemia compared to other antipsychotics and also have links with the development of insulin resistance, new onset type 2 diabetes mellitus and hypertriglyceridaemia (1, 4). After 6 weeks of treatment with olanzapine, Pillinger *et al.* demonstrated a statistically significant increase in body weight by 2.73 kg, body mass index by 1.07 kg/m^2, total cholesterol by 0.40 mmol/L, LDL cholesterol by 0.20 mmol/L and triglycerides by 0.46 mmol/L (1). It is unclear as to whether all these effects are mediated through weight gain; however there is evidence that hyperglycaemia and the early rise in triglyceride levels that occurs with olanzapine are independent of weight increase (2, 4).

At the onset of psychotic illness and before antipsychotic prescription, patients with schizophrenia have impaired glucose and lipid regulation (1). Hypertriglyceridaemia is also an independent risk factor for myocardial infarct, ischaemic stroke and vascular death (5). Thus, when certain antipsychotics are prescribed, it might make metabolic homeostasis worse in an already susceptible cohort. There have also been a number of case reports of olanzapine-induced hypertriglyceridaemia resulting in acute pancreatitis leading to multiorgan failure and death (6). These complications highlight the importance of metabolic screening prior to the commencement of antipsychotics and identifying individuals who may be at increased risk of severe hypertriglyceridaemia.

MFCS is a chylomicronaemia syndrome resulting from the coexistence of one or more secondary causes of hypertriglyceridaemia in a genetically susceptible individual. The most common secondary cause is undiagnosed or poorly controlled diabetes mellitus; however, in rare cases, olanzapine has been associated with this condition. In MFCS, and as evidenced in our case, once an individual's serum triglyceride level exceeds 5.65–7.91 mmol/L, clearance of triglycerides is saturated resulting in a sharp elevation in plasma triglyceride levels (3).

Though serum triglyceride levels encompass both chylomicrons and very-low-density lipoprotein (VLDL), hypertriglyceridaemia secondary to olanzapine is thought to be caused primarily by the accumulation of VLDL (7). Whether the elevation in VLDL is largely a result of increased production of VLDL, the reduction in excretion or both is still largely unknown and the focus of current research. Within 24 h of treatment with olanzapine, it has been shown to have effects on lipid biosynthesis enzymes and lipid metabolism within adipose tissue and the liver in mice (8). Whether this is a direct mechanism or secondary effect is still unclear; however, olanzapine-induced inflammation and reduction in adiponectin have been proposed as a mechanism for this observation (7). It has also been suggested that lipoprotein lipase deficiency may explain a proportion of patients who present with severe olanzapine-induced hypertriglyceridaemia, due to it being a major mechanism of triglyceride clearance (9). Current American guidelines recommend screening baseline weight, body mass index, blood pressure, fasting blood glucose and lipids prior to commencing an atypical antipsychotic (4). American and Australian guidelines suggest repeating fasting lipids at either 3 or 6 months after the commencement of atypical antipsychotics (4, 10); however, considering our case, repeating body weight, body mass index, fasting glucose and lipid profile 4 weeks after the commencement of olanzapine is recommended.

As demonstrated by our case, the prediction of who may be at risk of this significant drug effect may be difficult to determine. Our patient had no personal history of metabolic syndrome or obesity and had normal fasting serum lipids, blood glucose and HbA1c prior to the commencement of olanzapine. Pillinger *et al.* identified increased body weight, male sex and non-white ethnicity predict greater vulnerability to antipsychotic-induced metabolic dysregulation (1). Further research is required to determine specific patient characteristics that may identify patients at particular risk of MFCS. Once identified, these patients will likely require closer monitoring of serum lipids than current recommendations with the aim of early identification and subsequent prevention of cardiac and gastrointestinal complications.

Declaration of interest
We declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Author contribution statement
J R Greenfield is the physician of the patient; all other authors contributed equally to this case report.

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