

Case report: Olanzapine-induced acute pancreatitis and new diabetes mellitus

Erik Monasterio^{1*}, Ruchi Bhalla², Andrew McKean³

¹Department of Psychological Medicine, University of Otago, Christchurch, New Zealand

²Hammersmith and Fulham Mental Health Unit, West London Mental Health NHS Trust, London, UK

³Hillmorton Hospital, Christchurch, New Zealand

Email: *erik.monasterio@cdhb.govt.nz

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ABSTRACT

The aim of this case study is to review the literature and report the first published case of olanzapine-induced acute pancreatitis in New Zealand. A case report of acute pancreatitis with new onset diabetes mellitus secondary to olanzapine in a 42-year-old male, in the absence of medical risk factors is reported. Eleven previous case reports of olanzapine induced acute-pancreatitis were identified in the literature. A 42-year-old male was diagnosed with acute pancreatitis and new diabetes mellitus induced by olanzapine. Although rare, pancreatitis is associated with use of some atypical antipsychotic medications. It is important for prescribers to be aware of this potentially fatal side effect. In addition to this, we are highlighting the well documented evidence of metabolic disruption associated with olanzapine.

Keywords: Case Report; Olanzapine; Pancreatitis; Diabetes Mellitus

1. INTRODUCTION

Adverse side-effects associated with the use atypical antipsychotic medications (AAPs) are widely recognised; this has led to specific recommendations for regular side effect monitoring throughout a course of treatment [1,2]. Adverse outcomes include over sedation, metabolic derangement, extrapyramidal side effects, myocarditis, prolonged QTc interval, toxic megacolon and agranulocytosis [1-3].

The aim of this case report is to review the literature and describe the first published episode of olanzapine-induced pancreatitis in New Zealand.

Olanzapine was first funded in New Zealand in 1999/2000 by the Pharmaceutical Management Agency (PHARMAC). Its use was restricted by special authority

criteria and required application from a psychiatrist for a patient who had been trialled unsuccessfully on risperidone or required treatment with olanzapine short acting intra-muscular injection [4]. In June 2011, significantly cheaper generic versions of olanzapine were introduced and the special authority criteria for olanzapine withdrawn [5]. We aim to highlight lesser known and potentially fatal side effects through our case report.

2. CASE REPORT

Mr. X is a 42 year old man who had come into contact with mental health services on many occasions during the last two decades, due to recurrent depressive episodes. The clinical opinion over the years wavered towards low grade depressive and anxiety difficulties with Cluster B personality traits. From assessment notes dating back to 1994, it was noted that he had been prescribed doxepin 100 mg nocte for treatment of his depressive symptoms with its additional benefit of sedation. In 2006 he was commenced on olanzapine for its mood stabilising properties after he failed to respond to mood stabilising medications. At the time there was no clinical indication that he suffered from a psychotic illness.

In February 2010, four years after commencing olanzapine 10 mg daily, Mr. X became acutely medically unstable; he was transferred to a surgical ward following a twenty-four hour history of sudden onset, non-radiating abdominal pain, associated with nausea. He denied a history of gallstones or trauma. He had a minimal medical history of mild asthma. There was no past or present history of alcohol use or abuse. Although there was a family history of bipolar affective disorder affecting Mr. X's brother, there was no known family history of pancreatitis or type II diabetes mellitus.

On examination, Mr. X was tachycardic and tachypnoeic. Abdominal examination revealed mild distension with tenderness in the epigastrium and right upper quadrant. Air entry was decreased bibasally on chest auscultation. Blood tests indicated acute inflammation with a

*Corresponding author.

leukocytosis (white blood cell count 11.8; normal range $4 - 11 \times 10^9/L$) neutrophilia (neutrophil count 9.1; normal range $2.5 - 7.5 \times 10^9/L$) and raised C reactive protein of 43 (normal range < 10). Amylase was elevated at 358 (normal range $< 180 U/L$) with high lipase of 358 (normal range $7 - 60 U/L$). Urea and electrolytes (including calcium) liver function tests, including GGT and fasting triglycerides were all normal. Glycosylated haemoglobin was raised at 11.1% (normal range 6.5% - 7.4%). Chest radiograph showed patchy pulmonary opacity at the left lung base and atelectasis at the right lung base. Ultrasound imaging of the abdomen displayed an increase in liver echogenicity with no focal lesions and no evidence of gallstones. The pancreas, spleen and kidneys appeared normal.

The absence of any alcohol intake, trauma or gallstones, in addition to normal lipids, electrolytes and ultrasound imaging prompted a diagnosis of acute pancreatitis secondary to olanzapine. The patient was managed with supportive treatment of intravenous fluids, oxygen and analgesia. A secondary finding of new type II diabetes mellitus was established, and Mr. X was commenced on insulin and metformin. He made a good recovery, olanzapine was discontinued and outpatient diabetes follow-up was arranged.

When seen in Diabetes clinic four months later, glycosylated haemoglobin had fallen from 11.1% to 6.3%. At the time, Mr. X had been complaining of frequent dizziness, tiredness and hunger between insulin injections and especially overnight. The impression was that of hypoglycaemic events with rebound hyperglycaemia in the morning and evening. His insulin doses were reduced with Metformin maintained. On review by the same Diabetes specialist after another four months, glycosylated haemoglobin had fallen further to 6.0% and the insulin was stopped. Given the marked improvement in glucose control since olanzapine was stopped Mr. X was discharged from further Diabetic Outpatient follow-up. He has been under the care of his general practitioner and has maintained normal glucose levels with Metformin, 500 mg BD.

In December 2010, ten months after discharge from hospital, Mr. X was admitted for inpatient psychiatric care. He presented with symptoms of schizophreniform psychosis characterised by delusional beliefs of a persecutory nature with associated perceptual disturbances, of two months duration. He responded favourably to treatment with the antipsychotic agent amisulpiride 400 mg BD without evidence of metabolic impairment. He has been discharged from hospital and at 4 month follow-up his mental state and diabetic control have remained stable.

3. DISCUSSION

A PubMed search of olanzapine induced pancreatitis

revealed 11 case reports from 2000 to the current date [6-13] but no case reports in Australasia. There are no reports on doxepin-related pancreatitis from 1966 to the current date. Given the lack evidence in the literature for doxepin causing pancreatitis, and taking into consideration that Mr. X had been taking doxepin for 12 years before developing pancreatitis and has continued to take this after recovering from this condition, doxepin is unlikely to have played a role. In order to more clearly determine the likelihood that olanzapine caused the episode of pancreatitis in this case rather than an underlying disease or other factors, we have applied the Naranjo algorithm [14] (a logical evaluation procedure for determining the likelihood of an adverse drug reaction); we obtained a score of 5, which rates the likelihood as "probable". The mechanism by which olanzapine causes pancreatitis is unclear. A well recognised consequence of olanzapine use is hyperlipidaemia, which in itself is known to precipitate acute pancreatitis [1-3]. In 2007 Rossor *et al.* [8] described a case of chylomicronemia thought to be caused by olanzapine prescribed in a 36-year-old gentleman diagnosed with schizoaffective disorder. Six weeks after the introduction of olanzapine, he was diagnosed with acute pancreatitis with no other obvious risk factors. Interestingly, the patient described in our report had normal triglyceride serum levels. A 2000 correspondence article [10] and a subsequent case report [6] outline three cases of pancreatitis associated with significant alcohol intake, well beyond the national recommended guidelines. The authors proposed that olanzapine should be used in caution with patients who drink alcohol on a regular basis or who have a history of previous pancreatitis. Although in Mr. X and other reports [9,13] pancreatitis occurred more than one year after treatment, in most reported cases [8,9,15] pancreatitis occurred within six months of starting the medication. The Food and Drug Administration's Medwatch pharmacovigilance study of pooled, spontaneously reported adverse events revealed that of 192 patients who developed pancreatitis with one or more antipsychotic agents 40%, 33%, 16% and 12% were in patients receiving treatment with clozapine, olanzapine, risperidone and haloperidol, respectively; in 50% of patients treated with haloperidol they were also receiving an AAP medication; valproate was co-prescribed in 23% of patients; and 22 patients died [15]. In addition there have been a total of 26 reports of pancreatitis associated with olanzapine use to the UK MHRA spontaneous reporting scheme, with one fatality reported [16].

Our study highlights diabetes mellitus as another important complication of olanzapine therapy. Olanzapine induced diabetes mellitus is well documented in the literature [1-3,17]. A 2002 retrospective epidemiological study by Koller *et al.* [17] uncovered one hundred and

eighty eight cases of new-onset diabetes mellitus following the introduction of olanzapine. When it was discontinued or the dosage decreased, seventy-eight percent of patients had improved glycaemic control. Hyperglycaemia recurred in eight of ten cases with olanzapine rechallenge. This demonstrated a similar pattern of results in our patient, whose blood sugar levels markedly improved with the discontinuation of olanzapine. The exact cause of glucose dysregulation with olanzapine is unclear. It is hypothesised [18] that antagonism of 5-HT_{1A} (serotonin) receptors may decrease the responsiveness of pancreatic beta-cells, thus reducing insulin secretion precipitating hyperglycaemia. A recent study by Chiu *et al.* [19] looked at the time-dependent effects of olanzapine treatment in atypical antipsychotic naïve schizophrenic patients. The metabolic parameters were quantitatively assessed at zero, two, four and eight weeks by the intravenous glucose tolerance test. Insulin secretion significantly increased at week two, returned to baseline at week four and significantly increased again at week eight. The researchers concluded that olanzapine may directly influence pancreatic beta cell function to cause deficiency in insulin secretion, thus precipitating hyperglycaemia.

4. CONCLUSION

The aim of our report is to highlight a case of acute pancreatitis with new onset diabetes mellitus secondary to olanzapine, at a time when it is being removed from the New Zealand PHARMAC Special Authority funding list. We strongly anticipate a rise in its prescription in the community. The case of Mr. X highlights just how important this metabolic screening is, particularly in view of potentially fatal side effects such as acute pancreatitis and ketoacidosis. It is hoped that this report will alert clinicians to such consequences, with the aim to improve screening and reduce acute medical complications.

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