



Case Report: Pancreatitis Following Acute Overdose of Clozapine and Review of Possible Mechanisms Involved

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Abstract

Acute pancreatitis is a rare complication of clozapine use. While previous case reports have described pancreatitis from long-term use of clozapine, we present a case of pancreatitis from an acute overdose of clozapine in a young male patient. The patient improved with supportive treatment and transferred to a psychiatric institution subsequently. While the pathophysiology of antipsychotic-induced pancreatitis remains unclear, the effect of the drugs on serotonin receptors may be an important factor in the development of this disease.

Introduction

Atypical antipsychotics such as clozapine have various effects on pancreatic function resulting in metabolic abnormalities. While there are a number of case reports on acute pancreatitis from long-term use of clozapine [1-3], there are no reports of pancreatitis associated with single acute overdose of clozapine. In this report, we present a case of acute pancreatitis following acute overdose of clozapine.

Case Presentation

Mr P is a 26-year-old male. He has a background of schizophrenia on lithium (1.2 g every night), paliperidone (12 mg every morning), benztropine (4 mg twice a day) and zopiclone (15 mg every night as necessary). He was previously on clozapine (100 mg twice a day) but was stopped by his psychiatrist 3 months prior to presentation.

On the day of the presentation, his family found him unresponsive at home. Two empty strips of clozapine (20 tablets of 100 mg) were found near the patient. He also vomited once with the vomitus containing two tablets similar to clozapine. On examination, he was drowsy, with no coherent verbal response and only able to open eyes and move his limbs in response to stimuli. His blood pressure was 135/83 mmHg with a heart rate of 133 beats per minute. He was also mildly tachypneic with a respiratory rate of 18 and febrile at 38.2 degree Celsius. Cardiovascular and respiratory examination was normal. Tone was normal in all his limbs with but reflexes depressed.

Electrocardiogram shows sinus tachycardia with normal QT interval and random blood glucose was 6.7 mmol/L. Initial blood counts shows mild elevated white blood cell count and neutrophil count. Other differential counts are normal. Serum amylase was elevated at >2000 U/L, with no transaminitis hyperbilirubinemia. LDH was elevated at 582 U/L. Lipase was normal on day 1 of admission but increased to 123 U/L the following day.

Chest radiographs shows a left air space consolidation with pneumomediastinum. Computed tomography of the thorax demonstrated a defect in the distal oesophagus suggestive of rupture and swelling of the pancreatic tail and body. Initial diagnosis was that of acute clozapine overdose complicated by pneumonia, esophageal rupture and pneumomediastinum secondary to vomiting and acute pancreatitis.

Mr. P was intubated due to poor conscious level and admitted to the intensive care unit. Ultrasound of the hepatobiliary system shows no gallstones, cholecystitis or dilated common bile duct. A fasting lipid test done after transfer on day 10 also shows normal triglyceride level of 1.44 mmol/L. In addition to supportive treatment, Mr. P was started on intravenous antibiotics (ceftriaxone and metronidazole) for treatment of his pneumonia. He improved clinically in the intensive care unit and was transferred to the general ward on day four of his admission. He recovered well and was transferred to a psychiatric facility for further management (Figure 1).

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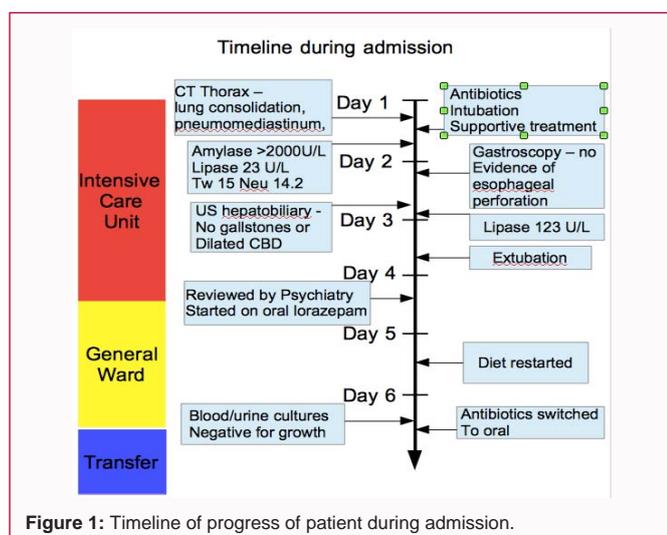
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Discussion

Previous case reports have described development of acute pancreatitis with chronic use of clozapine but there is no report of acute pancreatitis developing in an acute overdose of the drug. Although the patient was also on other psychotropic medications (lithium, paliperidone), we are not able to find any reports associating these other medications with acute pancreatitis [4]. A normal hepatobiliary ultrasound also excluded biliary obstruction as a possible etiology in the development of the pancreatitis.

Currently it is not known what is the main pathophysiological mechanism by which psychotropic induced pancreatitis is induced. Previous case reports have noted eosinophilia in patients, which suggest an allergic etiology [5,6], while others have postulated elevated triglyceride levels as a possible intermediately factor in the development of pancreatitis [7]. In our patient, both the eosinophil counts and triglyceride levels are normal, which suggests a more direct toxic exocrine effect on pancreatic tissue as suggested by other authors [8,9].

Effect of psychotropics on serotonin receptors in pancreatic tissue may be an important factor in the pathogenesis of drug-induced pancreatitis [10]. It is found that reduced levels of serotonin in murine pancreatic tissue reduced zymogen secretion which is an important step in the pathogenesis of pancreatitis, as well as directly increasing pancreatic cellular damage and fibrosis [11]. Individuals with certain haplotypes of HTR2C gene, which codes for the 5HT_{2C} serotonin receptor, are also found to have increased risk of metabolic abnormalities from clozapine and olanzapine [12]. The structural similarities between clozapine, olanzapine and quetiapine and the reported cases of acute pancreatitis in association with the chronic use of these three agents are to be noted as well [1,13,14]. Incidentally It is also known that these agents has significant higher binding affinity towards serotonin receptors with potent serotonin inhibitory effects which contribute to their pharmacological actions [15,16].

Why should an emergency physician be aware of this?

While there is still much unknown in the pathogenesis of clozapine induced pancreatitis, this case emphasizes the need for

clinicians to be alert to the possibility of pancreatitis in the patient presenting with an acute overdose of clozapine. More research is also needed to investigate the role of serotonin inhibition in the pathogenesis of psychotropic induced pancreatitis.

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