

Pancreatitis following Olanzapine Therapy: A Report of Three Cases

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Key Words

Pancreatitis · Atypical antipsychotic · Olanzapine · Drug induced pancreatitis

Abstract

Context: Atypical antipsychotic agents (clozapine, olanzapine) have been linked to metabolic effects and acute pancreatitis.

Case Report: We reviewed the inpatient and outpatient records of three patients who developed acute pancreatitis while being treated with olanzapine. The mean age of the patients was 37.7 years (range 18–54 years, 2 female, 1 male). No alternative cause of acute pancreatitis was found in two of the three patients. In the remaining patient, olanzapine may have contributed to acute pancreatitis in the setting of hypertriglyceridemia. Olanzapine was discontinued in all instances. Over a mean follow-up of 14 months, one patient has had a relapsing course, but the remaining two patients have been symptom free without recurrence of acute pancreatitis.

Conclusions: Our case series adds further support to the potential link between olanzapine use and acute pancreatitis. Close monitoring of metabolic parameters is suggested in patients treated with olanzapine. Alternative antipsychotic agents should be considered in patients at high risk for pancreatitis.

Introduction

Gallstones and alcohol are common etiologies of acute pancreatitis; rarer causes include hyperlipidemia, hypercalcemia, trauma, infection, and medications, among others. A definitive etiology is not immediately apparent in approximately 10% of cases, classified as idiopathic pancreatitis [1]. Increasing use of the MedWatch reporting system (<http://www.fda.gov/medwatch>) as well as heightened physician awareness have contributed to recognition of previously unknown adverse effects of routinely prescribed medications. Consequently, there is an emerging belief that some cases of presumed

idiopathic acute pancreatitis may be medication induced. Azathioprine, didanosine, pentamidine, and sulfonamides are most commonly implicated, but atypical antipsychotic agents have also been associated with acute pancreatitis [2].

Olanzapine (Zyprexa; Eli Lilly and Company, Indianapolis, Ind.), an atypical antipsychotic agent was developed after a precursor agent, clozapine, was found to be associated with agranulocytosis [3, 4]. Clozapine was initially linked to acute pancreatitis in 1992 [4, 5], and there has been concern that newer atypical antipsychotic agents, including olanzapine, could potentially also cause acute pancreatitis. At least three individual case reports have reported an association between olanzapine and acute pancreatitis [6–8], and a MedWatch surveillance system review [3] has also evaluated the connection. We report a series of three patients presenting with clinical and/or laboratory evidence of acute pancreatitis while being treated with olanzapine.

Patients and Methods

Over a period of 2 years, 3 patients (mean age 37.7 years, range 18–54 years, 2 females/1 male) referred for investigation and management of acute pancreatitis were noted to be taking olanzapine at presentation, and form the subjects for this case report. Inpatient and outpatient records were scrutinized to extract demographics, clinical presentation and hospital course. Outcome was assessed by office follow-up and telephone contact over a mean of 14 months (range 9–19 months). This case series was approved by the Human Studies Committee at Washington University School of Medicine. Informed consent was obtained from all patients.

Case 1

A 41-year-old Caucasian female presented with recurring episodes of acute pancreatitis dating back two years. She had no prior history of pancreatitis. She was taking olanzapine (5 mg/day) for depression, and the initiation of olanzapine preceded her first episode of pancreatitis by 3 months. She smoked half a pack of cigarettes a day, but she had no history of alcohol use. Over the next four months, she had several more episodes of acute pancreatitis culminating in a cholecystectomy. Pathologic examination of the cholecystectomy specimen did not reveal gallstones, sludge or cholecystitis. Three months after cholecystectomy, she developed two more episodes of pancreatitis, with lipase values peaking at 469 IU/l (normal range 0–60 IU/l). She was subsequently referred to our institution for further evaluation. Physical examination and routine laboratory testing did not reveal any abnormalities. Serum calcium level and lipid panel were within normal limits. A CT scan of the abdomen demonstrated mild dilatation of the extrahepatic bile ducts and an absent gallbladder, but no evidence of pancreas divisum or other structural pancreatic or biliary abnormality. An endoscopic ultrasound showed no causes for acute pancreatitis. Olanzapine was implicated and the medication discontinued. Over 19 months of follow-up, she has had relapsing abdominal pain, with at least one documented episode of acute pancreatitis. However, her pain episodes have been less frequent and less intense after olanzapine was discontinued.

Case 2

An 18-year-old African American female with childhood seizures and bipolar disorder was treated with olanzapine (10 mg/day) and sertraline. She presented with mid abdominal and left lower quadrant pain approximately two years later. She had no prior history of pancreatitis. She smoked a half pack of cigarettes a day and drank alcohol only on a social basis. On presentation, she had clinical and laboratory evidence of pancreatitis, with amylase of 195 IU/l (normal range 28–100 IU/l) and lipase of 418 IU/l (normal range 0–60 IU/l). Olanzapine was discontinued. Her course was complicated by *Clostridium difficile* colitis, and she required 19 days of inpatient management and total parenteral nutrition, but recovered fully. When seen several weeks later at our institution, her amylase and lipase levels had normalized. Work-up included an abdominal ultrasound, a CT scan of the abdomen, and an MRCP, all of which were normal and did not reveal a potential alternate explanation for her

pancreatitis. Olanzapine associated pancreatitis was considered, and she was counseled not to resume olanzapine. She has had no further episodes of pancreatitis off olanzapine in 14 months of follow-up.

Case 3

A 54-year-old Caucasian male with schizoaffective disorder treated with olanzapine (20 mg/day) for at least one year was admitted to a local hospital with three weeks of vomiting, abdominal pain, and poor appetite. Although his past history suggested hypertriglyceridemia with a pretreatment serum triglyceride value of 500 mg/dl, he had been compliant with fenofibrate therapy for the previous 18 months. He smoked one pack of cigarettes per day, and only consumed small amounts of alcohol socially. His other medications upon presentation included ziprasidone, mirtazapine, clonazepam and venlafaxine. On examination he was found to be jaundiced. An abdominal ultrasound revealed no gallstones, but the proximal common bile duct measured 9 mm in diameter. A CT scan demonstrated an inflammatory process at the pancreatic head, with peripancreatic inflammation. Olanzapine was discontinued and the patient referred to our institution for further management. Amylase, lipase, and CA 19-9 values were within normal limits. An ERCP revealed a distal common bile duct stricture with proximal ductal dilation. Endoscopic sphincterotomy, brushing of the stricture for cytology, and stent placement were performed; cytology was unremarkable. Subsequently, an endoscopic ultrasound revealed an inflammatory process in the head of the pancreas with surrounding lymphadenopathy. Olanzapine associated pancreatitis was considered, and the patient was advised not to resume this medication. The stricture resolved with conservative management. A repeat CT scan 6 months later revealed resolution of the pancreatic inflammation. No further episodes of pancreatitis have occurred over 9 months follow-up.

Discussion

In this report, we describe a series of three patients with idiopathic acute pancreatitis in temporal association with the use of olanzapine, an atypical antipsychotic agent. Careful and exhaustive clinical and laboratory evaluation failed to reveal a clear alternate etiology for acute pancreatitis in two patients. The remaining patient was under appropriate and adequate pharmacologic therapy for elevated triglycerides, and acute pancreatitis did not occur until after olanzapine was introduced. The authors believe that olanzapine was very likely a precipitating factor for acute pancreatitis in all these patients, especially since episodes diminished or resolved after the medication was withheld. While this association is difficult to conclusively establish, the possibility of this severe side effect may prompt additional caution in using olanzapine.

Atypical antipsychotic agents are used to treat a variety of conditions ranging from schizophrenia and acute mania to bipolar disorder and agitation, and off label uses for other psychiatric conditions are common. Clozapine was the first to be introduced in 1989, but agranulocytosis as a side effect has significantly curtailed its use. Olanzapine was developed as a replacement without the risk for agranulocytosis, and was approved by the Food and Drug Administration for clinical use in 1996. Commonly reported side effects with this medication consist of sleepiness, dry mouth, dizziness, restlessness, constipation, upset stomach, weight gain, increased appetite, and tremor. Potential severe adverse effects include extrapyramidal signs and symptoms [9]. A recent FDA review of 17 placebo-controlled studies of elderly demented patients treated with atypical antipsychotics suggested increased overall mortality with these agents when compared with placebo-treated groups, although the common causes of death were not different between the two groups [10]. Nevertheless, a black box warning was issued.

From a gastroenterologist's standpoint, acute pancreatitis is the most concerning association of atypical antipsychotic agents. Acute pancreatitis associated with clozapine was recognized when it was first introduced [4, 5]. Since 2000, there have been four cases of olanzapine associated pancreatitis reported in the literature [6–8]. The interval between initiation of olanzapine and onset of pancreatitis can be long, and has been reported to range from a few weeks to over 18 months [6–8], consistent with our observations. Therefore, patients who tolerate the medication in the short term could still develop pancreatitis after many months or even years. Our patients suffered from some of the severe complications of pancreatitis, including prolonged course, inflammatory phlegmon, and a relapsing course, suggesting that clinical course can be rough and potentially fatal. However, it is possible that the cases we describe represent the severe end of the spectrum of acute pancreatitis associated with olanzapine, since our institution caters to tertiary care.

Atypical antipsychotic agents are thought to exert their pharmacologic action through antagonism of dopamine and serotonin receptors, which results in lesser likelihood of extrapyramidal reactions compared to typical antipsychotics [11]. The mechanism for pancreatitis, however, is not clear. Ongoing research is focused on understanding the action of olanzapine on dopamine, serotonin, histamine, gamma-aminobutyric acid and adrenergic receptors in the mediation of adverse effects [12]. Atypical antipsychotic agents have been associated with weight gain, glucose intolerance, and development of type 2 diabetes in epidemiologic studies [13], and consequently, effects on glucose, triglyceride, insulin, and leptin metabolism are thought to contribute to adverse effects including pancreatitis [7]. The relationship between the global metabolic effects of atypical antipsychotics, including impaired glucose homeostasis, and direct pancreatic injury resulting in pancreatitis may reveal a common mechanism underlying both of these adverse effects. One longitudinal study over a five-year period documented an approximate doubling in serum triglyceride levels in patients treated with clozapine [14]. Similar increases in serum triglycerides have also been reported with olanzapine use [15, 16]. One of our patients had elevated triglyceride levels, but did not develop acute pancreatitis until olanzapine was initiated; further, he did not have a recurrence of acute pancreatitis after olanzapine was discontinued. This may suggest that patients with hypertriglyceridemia may further raise their triglyceride levels with these agents, thereby having a higher likelihood of pancreatitis when given this medication. If this hypothesis is true, patients being started on olanzapine may need to be screened for hypertriglyceridemia, and the medication avoided if this is found. It is unclear if patients with normal triglyceride levels will develop hypertriglyceridemia while on olanzapine, and further studies are needed. There is also mention in the literature of olanzapine acting synergistically with other known etiologic factors in causing acute pancreatitis, for instance, alcohol abuse [8].

Though little is known about olanzapine-associated pancreatitis, much study has been done on drug induced hepatotoxicity [17]. In the case of the liver, mechanisms of drug induced injury include disruption of intracellular calcium homeostasis, disruption of actin filaments, covalent modification of intracellular proteins, altered immunogenicity, activation of apoptosis, and mitochondrial disruption. It remains to be determined whether antipsychotic medication effects on the pancreas are mediated through direct

mechanisms as in the liver, or whether the effects are a consequence of global metabolic changes.

More study is required to further evaluate the effects of atypical antipsychotics on pancreatic function and pancreatitis. In addition to close monitoring for development of obesity and impaired glucose metabolism, it is prudent to exercise caution in treating patients at high risk for pancreatitis with these medications. This includes patients with elevated triglycerides, a prior history of pancreatitis, alcohol abuse, metabolic abnormalities and medications that increase the risk of pancreatitis. We agree with the suggestion by Waage et al. that patients on olanzapine should have frequent monitoring of blood work including pancreatic enzymes, particularly if they have one or more of the above risk factors for pancreatitis [7]. Patients who have tolerated the medication in the short term should not be viewed as being free from risk of pancreatitis. Furthermore, when patients present with pancreatitic and biliary disease of unclear etiology, careful evaluation and a high index of suspicion are necessary to determine if medications such as olanzapine may be contributing to the etiology of pancreatitis.

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