Acute Necrotizing Pancreatitis Following Olanzapine Treatment and 759C/T Polymorphism of HTR2C Gene: A Case Report

EMMANOUIL RIZOS1, KALLIOPI TOURNIKIOTI1, EVANGELOS ALEVZAKIS1, MELPOMENI PEPPA2, KONSTANTINOS PAPAZAXOS1, GEORGIOS ZORBAS3, IOANNIS MICHOPoulos1, IOANNIS LIAPPAS1, CHARALAMPOS PAPAGEORGIU1 and ATHANASIOS DOUZENIS1

1Second Department of Psychiatry, Attikon University Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece;
2Second Department of Internal Medicine-Propaedeutic, Endocrine Unit, Research Institute and Diabetes Center, Attikon University Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece

Abstract. Acute pancreatitis can be attributed to numerous potential causes, such as alcohol abuse, cholecithiasis, infection, lesions, tumors, hypercalcemia, hyperlipidemia, and medications. Among psychotropic medications, the use of some atypical antipsychotics, such as clozapine, olanzapine, quetiapine and risperidone, has been implicated in the development of acute pancreatitis, although the underlying mechanism has not been clarified. We describe the case of a young man with no other major medical problems, alcohol abuse or predisposing factors, who developed acute necrotizing pancreatitis following olanzapine administration, possibly through severe elevation of serum triglycerides. A pharmacogenomic analysis revealed the presence of the 5-hydroxytryptamine (serotonin) receptor 2C, G protein-coupled (HTR2C) -759C genotype which is related to increased risk for metabolic syndrome.

Acute pancreatitis can be attributed to numerous potential causes such as alcohol abuse, cholecithiasis, infection, lesions, tumors, hypercalcemia, hyperlipidemia, and medications. More specifically, hypertriglyceridemia constitutes the putative factor for 2-7% of the incidence of acute pancreatitis, while drug-induced incidence represents 0.1-2% of all cases (1). The occurrence of drug-induced acute pancreatitis is therefore a rare but potentially fatal adverse effect. Among psychotropic medications, the use of some atypical antipsychotics such as clozapine, olanzapine, quetiapine and risperidone, has been implicated in the development of acute pancreatitis, although the underlying mechanism has not been clarified. Here we describe the case of a young man with acute necrotizing pancreatitis induced by olanzapine administration, possibly through severe elevation of serum triglycerides.

Case Report

We present the case of a 22-year-old man with a diagnosis of schizophrenia who had been treated with olanzapine for 6 months at a dose regimen of 10 mg/day. The patient had no other major medical problems or any other psychiatric comorbidity. He had no pre-existing predisposing factors for pancreatitis such as alcohol abuse, past history of hypertriglyceridemia, or use of any other medication. The patient did not smoke and his bodyweight was within the normal range [body mass index (BMI): 25.8 kg/m2] with no weight increase during olanzapine treatment. His previous blood tests were normal and he had no family history for diabetes mellitus.

Six months after the initiation of olanzapine treatment, the patient presented with fever and severe epigastric pain and was admitted to the Internal Medicine Department. Laboratory tests, In addition to the elevation of serum amylase and total leukocytes, serum triglycerides were extremely elevated (>4,500 mg/dl) and an abdominal computed tomographic (CT) scan revealed the existence of multiple pancreatic pseudocysts, confirming the clinical hypothesis of acute necrotizing pancreatitis. During his admission, the patient developed acute respiratory insufficiency and metabolic acidosis and was transferred to...
the Intensive Care Unit. Olanzapine administration was interrupted. A lung CT scan showed diffuse lung infiltrations and his clinical picture was complicated by the onset of hyperglycemia, with glycosylated hemoglobin A1c of 14.6%. The patient was put on mechanical ventilation and was subjected to regular insulin infusion and appropriate antibiotics. Progressively, his condition was stabilized and he was started on 800 mg/day amisulpride without any further complication. After one month of hospitalization, the patient's laboratory examinations were within normal range. The serum triglyceride level was 197 mg/dl; fasting and postprandial blood glucose were normal, with a glycosylated hemoglobin A1c test of 10.2%, without need for continuation of insulin or other antidiabetic treatment. Furthermore, a new lung and abdominal CT scan documented amelioration, with the presence of a sole small pancreatic pseudocyst. The patient was discharged from the hospital in good physical condition.

Shortly after his discharge, we performed pharmacogenomic analyses of enzymes of cytochrome P450: CYP2D6, CYP1A2, CYP3A5 which are involved in antipsychotic drug metabolism and drug-induced side-effects (specifically extrapyramidal), as well as of the serotonin 2C receptor (HTR2C) whose polymorphisms are related to the development of metabolic syndrome in schizophrenic patients treated with atypical antipsychotics. The analyses results showed no abnormal cytochrome P450 polymorphisms but revealed the presence of the HTR2C -759C genotype.

Discussion

Olanzapine can predispose to the development of hypertriglyceridemia, hyperglycemia, hyperlipidemia and weight gain. In fact, there is evidence of an approximate doubling of serum triglyceride levels in patients treated with olanzapine (2, 3), although increases as marked as that observed for our patient are rare. Despite intense basic and clinical research, the nature of the pathogenesis of pancreatitis remains largely unknown. However, it seems that in our case, severe hypertriglyceridemia with serum levels >1,000 mg/dl might have predisposed to pancreatitis. In fact, when triglyceride levels are elevated, chylomicrons tend to be present, and may obstruct capillaries, leading to pancreatic inflammation and pancreatitis. Moreover, excess free fatty acids from triglycerides may generate further cytotoxic injury, releasing inflammatory mediators and aggravating the pancreatitis (4).

Researchers have suggested that pancreatitis is better understood as a spectrum of a syndrome whose heterogeneous nature derives from the complex interplay between lifestyle factors (e.g. diet and medication), genetics and resultant differences in pathophysiology (5). Given the temporal association and the absence of other known risk factors, the onset of acute pancreatitis in our patient is most likely attributable to the intake of olanzapine. Using the causality scale of Naranjo et al., pancreatitis qualified as a probable adverse drug reaction to olanzapine (6). Furthermore, most cases of antipsychotic-induced acute pancreatitis occur within six months of treatment and more often in males (7).

Since 2000, several cases of olanzapine associated pancreatitis have been reported (8-10), among which there is only one report of acute necrotizing pancreatitis (11). However, in some cases, other predisposing factors such as alcohol abuse were present. Moreover, it remains unclear whether the effect of olanzapine on the pancreas may be mediated through direct drug-induced injury as in the liver, or whether it represents the consequence of global metabolic changes, in particular triglyceride elevation (12).

Although the exact mechanism of causation of hyperlipidemia by olanzapine is unknown, the disruption of hypothalamic regulation of serum glucose levels, potent anticholinergic activity, 5-HT2C antagonism, hyperprolactinemia and leptin resistance may be involved in the pathogenesis. In our patient, the presence of the 759C/T polymorphism of HTR2C gene possibly underlines a genetic predisposition to the adverse metabolic effects of olanzapine. Specifically, the 759C/T HTR2C genetic polymorphism and in particular lower frequency of the T variant has been associated with abnormalities of fasting levels of glucose, total cholesterol, low-density lipoprotein and triglycerides in blood, although there are contradictory results in association studies (13-15).

In conclusion, we hypothesize that the aforementioned polymorphism may have led to susceptibility to extreme triglyceride elevation following olanzapine treatment and consequent pancreatic injury. Clinicians need to be alert and improve screening in order to reduce drug-induced complications. In the future, genetic testing could contribute to better prescribing decisions.

References

5 Tenner S: Molecular biology, epidemiology, and the elusive nature of pancreatitis. Clin Transl Gastroenterol 6: e80. doi: 10.1038/ctg.2015.1
Rizos et al: Pancreatitis, Olanzapine and -759C/T Polymorphism of HTR2C Gene


Received June 29, 2015
Revised July 22, 2015
Accepted July 24, 2015