Case report: acute pancreatitis induced by Clozapine


Abstract

Two percent of acute pancreatitis are drug induced. In the present paper, we reported the case of a 39 year-old patient with chronic-hallucinatory schizophrenia who developed symptomatic pancreatitis during the clozapine dose titration performed to reach the therapeutic range. Diagnosis of pancreatitis was suggested by clinical examination and abnormal laboratory values of pancreatic enzymes and confirmed by C-T scan and ultrasonography. The causal incrimination of clozapine in this case seems likely as all other possible causes of pancreatitis were excluded, as AP developed shortly after the introduction of the drug and as the pancreatic enzymes normalized after clozapine was stopped. No rechallenge to confirm the causal relationship was however attempted. So far, only eight cases of acute pancreatitis have been reported in association with clozapine use. Clozapine is an atypical antipsychotic drug which belongs to the chemical class of dibenzodiazepines. The mechanism by which clozapine could produce acute pancreatitis remained unclear. Nevertheless, we advocate a careful biological follow-up (measuring periodically the concentrations of amylase, lipase and triglycerides) during the treatment by clozapine. (Acta Gastroenterol Belg., 2005, 68, 92-94).

Key words: Acute pancreatitis, clozapine, drug-adverse effect.

Introduction

The annual incidence of acute pancreatitis (AP) is over 23 cases per 100,000. Approximately 20% disclose a severe course and 5 to 10% will lead to death (1). Alcohol and gallstones represent the two major causes of AP whereas drugs are implicated in around 2% of cases (2). Clozapine is a dibenzodiazepine used for its potent antipsychotic effect among resistant forms of schizophrenia. It has exceptionally been reported as a cause of AP ranging from mild to severe (3). Clozapine implementation was maintained till 200 mg/day clozapine (day 14). After day 14, the abdominal pain and vomiting episodes become however more and more frequent. A laboratory tests performed at day 23 showed elevated leukocytes at 19,900/mm³, elevated serum amylases at 703 IU/L (normal value < 100), lipases at 842 IU/L (normal value < 60) whereas liver tests were within normal values. Clozapine implementation was maintained till 200 mg/day clozapine (day 14). After day 14, the abdominal pain and vomiting episodes become however more and more frequent. A laboratory tests performed at day 23 showed elevated leukocytes at 19,900/mm³, elevated serum amylases at 863 IU/L (normal value < 100), lipases at 1256 IU/L (normal value < 60) whereas liver tests were within normal values. The clozapine was immediately lowered to 100 mg/day and a contrast enhanced CT-scanner was performed. It showed diffuse enlargement of the pancreas with a 19-millimeter in diameter hypodense area suggestive of necrosis in the head. Neither the CT-scan or the abdominal ultrasound showed abnormality of the liver or the biliary tract. The 24th day, amylase and lipase values began to diminish progressively. Ten days later, a CT-scan showed cystic formation in the head and the tail of the pancreas. Clozapine was then definitively stopped.

Case Report

At the age of twelve, the patient presented his first aspecific pre-morbid behavioral disturbances. These consisted in intense aggressive behavior and progressive social withdrawal. Paranoid schizophrenia diagnosis was established five years later because of severe psychotic symptomatology including persecutory delusions, auditory hallucinations and episodes of agitation with physical aggressiveness. During the next 25 years, classical antipsychotics stabilized the disease despite some short relapses related to discontinuation of treatment. At the age of thirty-two, the patient disclosed psychotic symptoms in spite of several changes in antipsychotic medication. Clozapine was started for this resistant form of schizophrenia at the initial dosis of 25 mg per day, progressively increasing 25 mg/day every two days up to 200 mg/day at the 15th day. Other psychotropic drugs (clozapine, sulpride, levopromazine, dehydrobenzperidol, haloperidol, lorazepam) and trithioparamethoxyphenylpropen were maintained. There was no daily alcohol intake. The concentrations of cholesterol and triglycerides were in normal limits. As usual, leukocytes differential count was monitored to prevent agranulocytosis. On the 6th day of clozapine treatment, the patient developed slight abdominal discomfort, nausea and few episodes of vomiting; at that time he was under 100 mg/day of clozapine. Laboratory tests was then performed and showed 12,800/mm³ leukocytes, elevated serum amylases at 703 IU/L (normal value < 100), lipases at 842 IU/L (normal value < 60) whereas liver tests were within normal values. Clozapine implementation was maintained till 200 mg/day clozapine (day 14). After day 14, the abdominal pain and vomiting episodes become however more and more frequent. A laboratory tests performed at day 23 showed elevated leukocytes at 19,900/mm³, elevated serum amylases at 863 IU/L (normal value < 100), elevated lipases at 1256 IU/L (normal value < 60) and elevated CRP 22 mg/dl (normal value < 1) whereas liver tests were within normal values. The clozapine was immediately lowered to 100 mg/day and a contrast enhanced CT-scanner was performed. It showed diffuse enlargement of the pancreas with a 19-millimeter in diameter hypodense area suggestive of necrosis in the head. Neither the CT-scan or the abdominal ultrasound showed abnormality of the liver or the biliary tract. The 24th day, amylase and lipase values began to diminish progressively. Ten days later, a CT-scan showed cystic formation in the head and the tail of the pancreas. Clozapine was then definitively stopped.

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Discussion

To prove that acute pancreatitis (AP) is drug-induced requires three imputability criterions: 1) AP development during the treatment with the drug, 2) exclusion of other causes of AP mainly biliary or alcoholic, 3) AP recovery after drug withdrawal and AP recurrence after rechallenge with the drug (4). Drug imputability is qualified “highly probable” when these three criteria are present. Nevertheless, rechallenge test is rarely performed for ethical reasons, and the drug is then labeled as “possible” etiologic factor (3). In our report, the first two criteria were fulfilled. Rechallenge test was not performed because of the potential severity of a further access of AP. Clozapine can reasonably be considered as causal factor because of the tight temporal relation between the AP episode and clozapine introduction and the exclusion of other classical causes of AP.

AP is a very rare complication of clozapine treatment. To our knowledge, only eight other cases have been reported to date in the literature (5-12).

Martin (5) described the case of a 40 year-old man who presented an elevation of amylase and lipase level after 8 days of clozapine treatment. The pancreaticobiliary tree was normal and there were no evidence of gallstones. Frankenburg (6) reported the case of a 17 year-old woman who presented abnormal levels of amylase and lipase, eosinophilia along with pyrexia, right upper quadrant pain, nausea and vomiting after two weeks of institution of clozapine. These clinical and biological abnormalities remitted after cessation of clozapine but recurred 30 days later after two weeks of re-treatment. The patient was also taken valproic acid, before and after clozapine treatment and didn’t present then, abnormalities of pancreatic enzymes. Jubert (7) reported a case of severe acute pancreatitis following the ingestion of 1000 mg of clozapine in a suicidal attempt perpetrated by a 63 year-old woman who arrived at the hospital in a coma. The diagnosis was supported by the presence of hyperamylasemia, hyperamylasuria and an elevated serum lipase levels and the ultrasonographic images. Because no other causes have been found and, on the basis of the temporal relation, the pancreatitis was attributed to clozapine treatment. Fullerton (8) reported a case of acute pancreatitis, 24 hours after administration of 450 mg/day of clozapine in a 52 year-old black woman with no past medical history of relevance and no history of alcohol abuse, gallstones or other unexplained abdominal symptoms. Fullerton (8) reported a case of acute pancreatitis, 24 hours after administration of 450 mg/day of clozapine in a 52 year-old black woman with no past medical history of relevance and no history of alcohol abuse, gallstones or other unexplained abdominal symptoms. Fullerton (8) reported a case of acute pancreatitis, 24 hours after administration of 450 mg/day of clozapine in a 52 year-old black woman with no past medical history of relevance and no history of alcohol abuse, gallstones or other unexplained abdominal symptoms. Fullerton (8) reported a case of acute pancreatitis, 24 hours after administration of 450 mg/day of clozapine in a 52 year-old black woman with no past medical history of relevance and no history of alcohol abuse, gallstones or other unexplained abdominal symptoms.
Our patient as the cases described before presented elevated amylase and lipase levels only after the introduction of clozapine. He had no prior abdominal complaints or risk factors to develop pancreatitis. The diagnosis of acute pancreatitis was confirmed by C-T Scan and ultrasonography. No other possible cause of pancreatitis could be found. During the acute phase the clozapine dose was lowered to 100 mg/day but definitely stopped after a control C-T Scan three weeks later because of cystic transformation in the head and tail of the pancreas.

Pathogenesis of drug-induced pancreatitis has not yet been clarified. Among many hypotheses, the most widely accepted suggests that peripheric pancreatic duct rupture results from duct blockage (e.g., by increased viscosity of pancreatic juice). Proenzymes are then released, leading to autodigestion of the gland. Drugs might also alter the process of zymogen granule formation or exocytosis (13-14), leading to proenzymes activation within the cell and subsequent autodigestion (15-16). Drugs might also affect this cellular process (15).

Clozapine [8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo(b,e)(1,4)diazepine] belongs to the chemical class of dibenzodiazepines, related chemically to the antipsychotic dibenzoazepine drug loxapine. Clozapine has considerable serotonin (S2), alpha1-adrenergic and histaminergic (H1) blocking activity and is also a potent muscarinic acetylcholine receptor antagonist (17). Its binding to both D1 and D2 receptors is less pronounced and relatively more balanced than that on classical antipsychotics (17). Its binding to both D1 and D2 receptors is less pronounced and relatively more balanced than that of typical neuroleptics. Clozapine has been shown to improve 30% of the patients refractory to antipsychotic drugs (18). Although the well-known side effects of clozapine are agranulocytosis, increased risk of seizures, and initial sedation, other rare and less known complications have been reported, such as transient leukocytosis or eosinophilia, cardiorespiratory arrest, sudden death, and gastrointestinal disorders. The drug is 95% protein-bound and bioavailability is not affected by food. Clozapine is eliminated principally by the hepatic P-450 1A2 and 3A4 cytochrome enzymes and the elimination half-time is 14 h. The standard dose range is 300-600 mg/day although doses up to 900 mg/day may be used in treatment-refractory patients. Clozapine could, like other drugs, have a toxic effect on the pancreas. Another consideration is that patients treated with clozapine are generally resistant to classical antipsychotics, and received high doses of other medication. Even if the drugs used are not known to induce solely pancreatitis it might be possible that their interactions with clozapine might have this effect. Finally it is possible that patients on clozapine treatment present a transient elevation of amylase and lipase levels and that very few of them present a severe AP. The mechanism by which this might happen deserves further studies. Meanwhile it seems to us advisable to monitor weekly amylase and lipase during step-by-step increasing phase and to control periodically weight, glycaemia, triglyceride levels, amylase and lipase in all patients treated by clozapine.

References