A Case of Clozapine-Associated Pancreatitis

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Abstract: Acute pancreatitis is a very rare complication of clozapine treatment. We report a new case of symptomatic pancreatitis subsequent to starting of clozapine treatment. In this case, the diagnosis of pancreatitis can be considered definitive and the etiological link between clozapine and pancreatitis highly likely. Recovery was not complete. In a 10-year period, we treated 363 cases (196 patients) with clozapine. We diagnosed clozapine-associated pancreatitis only in this patient. However, we did not check amylase and lipase plasma levels in all patients and possibly missed several cases of pancreatitis. We suggest monitoring pancreatic enzymes routinely, at least in the first months of clozapine therapy.

Keywords: Antipsychotics, clozapine, pancreatitis, side effects.

INTRODUCTION

Between 2 and 5% of cases of acute pancreatitis are drug related [1]. Drugs cause pancreatitis either by a hypersensitivity reaction or by the generation of a toxic metabolite. The autodigestion by proteolytic enzymes activated in pancreas rather than in the intestinal lumen is the suspected pathogenic mechanism. Rechallenge tests, consistent case reports, animal experiments, data on the incidence in drug trials provide evidence of a definite association with pancreatitis for didanosine, valproic acid, aminosalicylates, estrogen, calcium, anticholinesterases, and sodium stibogluconate. An association with pancreatitis is likely, but not definitely proven, for thiazide diuretics, pentamidine, ACE inhibitors, asparaginase, vinca alkaloids, nonsteroidal anti-inflammatory drugs, and clozapine [2]. In a pharmacovigilance study of spontaneously reported adverse events [3], 192 patients developed pancreatitis during antipsychotic treatment. Most cases of pancreatitis occurred within 6 months after the start of antipsychotics. Of the reports of pancreatitis associated with antipsychotics, 40%, 33%, 16%, and 12% were in patients receiving clozapine, olanzapine, risperidone, and haloperidol, respectively. In 50% of the patients receiving haloperidol, an atypical antipsychotic was listed as a concomitant drug. Valproate was administered concomitantly in 23% of patients.

Acute pancreatitis is a very rare complication of clozapine treatment [4]. In the literature, a total of 14 cases of clozapine-induced pancreatitis have been published so far [5]. The pathogenesis of clozapine-associated pancreatitis is unknown. Sani *et al.* [5] hypothesize that the same mechanism, which has been advanced to explain clozapine agranulocytosis, may fit better to pancreatitis, i.e. clozapine-induced formation of an unstable nitrenium^{+} metabolite that in turn induces apoptosis and activation of cytokines and immunoglobulins.

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We report a new case of symptomatic pancreatitis subsequent to starting of clozapine treatment.

CASE REPORT

A 40-year-old man with schizoaffective disorder, bipolar type, was admitted to the Psychiatric Intensive Care Unit (PICU) of a General Hospital for psychotic relapse. He had been treated with haloperidol decanoate 150 mg i.m. every 3 weeks (last dose 20 days before admission). The patient did not present symptoms of any other medical illness. In childhood, he had suffered from pielonephritis and had undergone appendicectomy. He did not drink alcohol. Urine toxic screening (including alcohol) was negative. He was 165 cm tall and weighed 69.5 kg (body mass index: 25.5 kg/m^2). On admission, routine laboratory (not including amylase and lipase plasma levels) was normal. Blood glucose was 81 mg/dL (normal range [NR]: 76-110), serum triglycerides were 109 mg/dL (NR: 50-200). He presented hallucinations, delusions, mood depression, suicidal ideation, negative symptoms, akinesia, and akathisia. On admission, he asked another patient to be strangulated. Two days after, he cut his wrists with a shuttered mirror. We started clozapine and titrated it up to 100 mg in the morning and 175 mg at bed time on the 18th day of hospitalization. We started lithium, 300 mg t.i.d., on the 7th day of hospitalization, and added risperidone, 2 mg at bed time, in the first 10 days of clozapine titration. The patient improved. Hallucinations, delusions of guilt and ruin, and suicidal ideation vanished. The intensity of other delusions lessened. Significant side effects were hyper salivation, constipation, and transient tachycardia. Complete Blood Count (CBC) presented a mild granulocytosis. On the 18th day of hospitalization, the patient complained of abdominal pain, without nausea or vomiting. His abdomen was meteoric, tractable, mildly aching. He evacuated abundant, semi-solid, normochromic feces. Body temperature was 36.5°C. Laboratory analysis showed 25.1 (10^3/uL) White Blood Count (WBC), neutrophils 22.2(10^3/uL) (88.7%), amylase plasma level 1050 U/L (NR: 5-100), AST 41 U/L (NR: 2-38), ALT 59 U/L (NR: 2-41), glucose 146 mg/dL (NR: 76-110), urea 52 mg/dL (NR: 10-50), creatinine 1.6

1876-5238/11

(mg/dL (NR: 0.6-1.20), Ca 14.14 mg/dL (NR: 8.6-10.5), P 6.6 mg/dL (NR: 2.7-4.5), Na 135 mEq/L (NR: 136-146), K 4.85 mEq/L (NR: 3.5-5.1), Cl 95 mEq/L (NR: 98-110), total bilirubin 1.12 mg/dL (NR: 0.20-1.19), conjugated bilirubin 0.42 mg/dL (NR: 0.05-0.3). The results of CBC, triglycerides, amylase and lipase plasma levels are shown in Table **1**. Eosinophilia was never present. A plain abdomen film revealed gas distention of right and descending colon and of an ansa of the small intestine in the superior, left quadrant ("sentinel loop"), and gas distention of the gastric bubble. Five hours later, a plain abdomen film revealed air-fluid levels in the transverse colon, reduction of the colonic gas distention, and a dilated ansa of the small intestine in the pelvis. An abdominal sonography revealed liver enlargement, normal gallbladder, spleen, and kidneys. Pancreas was not observable for bowel gas. Clozapine and lithium were withdrawn, and oral alimentation was prohibited. Fluid therapy, somatostatine 0.1 mg t.i.d., gabexate 400 mg i.v., omeprazole 100 mg i.v., and ceftriaxone i.v., 1 g. b.i.d were started. In the following 3 days, clinical condition remained stable. Abdomen was tractable, not aching upon palpation. Alveus was open to gas and feces. An abdominal sonography revealed a dilated gallbladder, full of dense bile and biliary sand. Major biliary tract diameter was at upper normal limits (5 mm). Only a part of pancreas was visible, which showed fine inhomogeneous structure, without focal lesions. Six days after the beginning of pancreatitis, a sonography revealed gallbladder distention (transverse diameter: 5 cm), containing mobile, layering sludge echogenic material, wide distension of the main biliary tract (7 mm), and a mild distension of the left intra-hepatic biliary duct. The pancreas appeared normal, without distension of major ducts. Patient's general condition remained good. He was afebrile. His abdomen was tractable and not aching. Alveus remained open to gas and feces. The patient was referred to a surgical ward where he underwent cholecystectomy, with progressive improving. Ten months after discharge, the patient was admitted again to the PICU for psychotic relapse. He was treated with haloperidol decanoate 100 mg i.m. (last dose 5 days before admission), risperidone 4 mg/day, and valproate 500 mg/day. On admission, pancreatic amylase plasma level was 215 U/L (NR:15÷53). Otherwise, laboratory was normal. Temperature was 36.5°C. He had no pain. His abdomen was tractable. Urine toxic screening (including alcohol) was negative. Valproate plasma level was 26.52 μg/mL (therapeutic range:50÷100). We withdrew valproate and treated him with risperidone 6 mg at bed time, and ox-carbazepine, 1200 mg/day. WBC, triglycerides, amylase and lipase plasma levels are shown in the table. Abdomen sonography was normal, with evidence of past cholecystectomy. Seven days later, the patient was discharged improved with diagnosis of schizoaffective disorder, bipolar type and of chronic pancreatitis.

DISCUSSION

In this case, the diagnosis of pancreatitis can be considered definitive. We excluded alternative diagnoses (e.g., perforated viscus, acute cholecystitis, intestinal obstruction, etc.). Amylase plasma levels greater than three times normal are indicative of pancreatitis. The temporal relation between pancreatitis and starting of clozapine therapy strongly suggests a causal relationship. The relation between concomitant drugs and pancreatitis seems negligible, although it cannot be excluded definitively. Risperidone had been withdrawn 8 days before onset of pancreatitis. However, WBC rose a few days before amylase levels did and before the diagnosis of pancreatitis was made (18^{th} day). This could be the first lab indication of incipient pancreatitis related to risperidone. The association between lithium with pancreatitis is remote. In Medline, there is only one report about possible or probable causal link between lithium and pancreatitis [6] and only one report of alterations in the serum concentrations of calcium, parathyroid hormone, and amylase without features of acute pancreatitis, during an intoxication with lithium [7]. Regarding haloperidol, it had been well tolerated by the patient for years, and its plasma level was decreasing. Furthermore, we excluded alternative common causes of pancreatitis such as gallstones, alcohol abuse, hyper-triglyceridemia, endoscopy retrograde cholangiopancreatography, trauma or previous surgery, by history, echography, plain abdomen film, and laboratory tests. However, the etiological link between clozapine and pancreatitis, although highly likely, cannot be considered definitive because there was no rechallenge to clozapine in patient's follow-up.

Differently from Frankenburg and Kando [8], Chengappa *et al*. [9] and Garlipp *et al*. [10], we did not observe eosinophilia, but this abnormality is by no means the rule with clozapine-associated pancreatitis. Differently from the cases reported by Bergemann *et al*. [11], Garlipp *et al.* [10], and Sani *et al.* [5], our patient was symptomatic, as the other eleven cases reported in the literature.

The presence of dense bile and biliary sand is problematic, since the relationship between gallstones and susceptibility to clozapine-associated pancreatitis is unclear. Chengappa *et al.* [9] reported cholelithiasis in their patient who underwent cholecystectomy. Huang's *et al.* [12] report of pancreatitis with clozapine several years after cholecystectomy suggests that a lithiasic tendency could predispose to clozapine-induced pancreatitis. Schmitz-Hübsch *et al.* [13] reported the case of a patient with gallstones who developed recurrent pancreatitis with clozapine. After cholecystectomy, there was no evidence of pancreatitis after clozapine rechallenge. It is not clear whether cholecystectomy aided recovery in our patient since he was already improving before surgery. Unfortunately, recovery was not complete. Although the patient was asymptomatic in the course of his second admission to the PICU, high amylase levels documented chronic pancreatitis.

In a 10-year period, we treated 363 cases (196 patients) with clozapine. We diagnosed pancreatitis in two of them. In one case, we considered pancreatitis induced by alcohol intoxication and/or concomitant valproate treatment. Actually, this patient withdrew valproate and continued clozapine treatment without any further evidence of pancreatitis. Therefore, the incidence of pancreatitis induced by clozapine seems low. However, we did not check amylase and lipase plasma levels in all patients. As Greenberger & Toskes [1] claim, manifestations of pancreatitis are multiform. If the clinician suspects pancreatitis only in presence of the typical symptoms of the disease, s/he will miss most cases of pancreatitis. Although rare, clozapine associated pancreatitis can have a severe or ominous outcome. We suggest to monitor

Table 1. The Results of CBC, Triglycerides, Amylase and Lipase Plasma Levels are Shown

First admission. Date	**WBC** (10^3/uL)	**Neutrophils** (%)	**Neutrophils** (number)	**Amylase** (U/L) (laboratory normal range:0-100)	**Lipase** (U/L) (laboratory normal range: 5-60)	**Triglycerides** (mg/dL) (laboratory normal range: 50-200)
2nd day	6.2	60.0	3.7			109
7th day	10.0	74.0	7.4			
12th day	16.6	84.9	14.2			
14th day	14.7	80.1	11.8			
18th day	25.1	88.7	22.2	1050		
19th day	14.2	74.2	10.6	675	25	
20th day	11.0	80.2	8.9	502	81	
21st day	10.9	75.4	8.3	795	250	
22nd day	13.8	81.2	11.3	1080	431	
23rd day	11.0	76.2	8.4	909	494	126
24th day	8.4	68.2	5.7	788	234	
Second admission. Date	**WBC** (10^3/uL)	**Neutrophils** (%)	**Neutrophils** (number)	**Amylase** (U/L) (laboratory normal range:15-53)	**Lipase** (U/L) (laboratory normal range: 0-60)	**Triglycerides** (mg/dL) (laboratory normal range: 50-170)
2nd day	5.9	59.1	3.5	215	33	109
3rd day				221	26	
4th day				213	34	
7th day				213		

pancreatic enzymes routinely, at least in the first months of clozapine therapy.

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