

CASE REPORT

Indomethacin-Induced Pancreatitis: A Case Report

Dilek Memis, Esin Akalin, Tuba Yücel

Department of Anesthesiology, Medical Faculty, Trakya University. Edirne, Turkey

ABSTRACT

Context There are no previous reports of acute pancreatitis associated with the use of indomethacin in the general population. Drugs of all types are related to the etiology of pancreatitis in approximately 1.4-2.0% of cases.

Case report We report the case of a 56-year-old man who presented with acute pancreatitis after a period of indomethacin therapy. Other causes of the disease were ruled out. Due to multiorgan failure, he was in the intensive care unit for 44 days. He made a full recovery. The indomethacin was discontinued.

Conclusions We report indomethacin as the probable cause of acute pancreatitis in a patient without any known predisposing factors. To our knowledge, this is the rare description of a case of indomethacin-induced pancreatitis. However, the link is difficult to establish and further evidence is required to prove the association.

INTRODUCTION

Few data exist about the incidence of drug-induced pancreatitis in the general population. Drugs are related to the etiology of pancreatitis in about 1.4-2.0% of cases [1, 2]. Indomethacin is a potent inhibitor of prostaglandin-forming cyclooxygenase; it also inhibits the motility of polymorphonuclear

leukocytes. The anti-inflammatory effects of indomethacin are evident in patients with rheumatoid and other types of arthritis. Indomethacin has analgesic properties distinct from its anti-inflammatory effects [3]. Pancreatitis is a very rare adverse effect and few cases of indomethacin-induced pancreatitis have been reported in the literature until now [4]. We report on a case of indomethacin-induced pancreatitis in a man who had always been in good physical health.

CASE REPORT

A 56-year-old man presented to the Accident and Emergency Unit with a one day history of severe abdominal pain of sudden onset radiating to the back, plus nausea and vomiting, followed by a comatose state, areflexia, seizures, severe hypotension and hypoxia. He had no previous surgical history, no history of alcohol use and no history of trauma. He had only used indomethacin (150 mg/day orally) for three weeks for arthritis. On physical examination, the patient's abdomen was distended and diffusely tender. His bowel sounds were reduced. Rectal examination proved negative. Blood tests revealed an amylase level (2,950 IU/mL, reference range: 0-180 IU/mL), a raised white cell count ($47.9 \times 10^9/L$, reference range: $4-11 \times 10^9/L$), alanine aminotransferase (SGOT: 143 IU/L, reference range: 15-41 IU/L), lactic dehydrogenase (282 IU/L, reference range: 98-192 IU/L) and elevated C-reactive protein level (22 mg/L, reference range: 0-10 mg/L). Serum values of urea, creatinine, alkaline

Table 1. Laboratory parameters.

	Value	Reference range
Amylase (IU/mL)	2,950	0-180
Leucocytes (x10 ⁹ /L)	47.9	4-11
Glucose (mg/dL)	245	75-115
Serum LDH (IU/L)	282	98-192
SGOT (IU/dL)	143	15-41
C-reactive protein (mg/L)	22	0-10
Hematocrit (%)	51.2	35-45
Serum Ca ²⁺ (mg/dL)	8.5	8.5-10.3
Arterial PO ₂ (mmHg)	56	70-85
Base deficit (mmol/L)	-6.5	-3 - +3

phosphatase, triglycerides, cholesterol, calcium and bilirubin were within reference limits. Laboratory parameters are shown in Table 1.

The workup for pancreatitis included an ultrasound which demonstrated that the patient had a normal liver, small gallstones in a normal gallbladder with no evidence of common bile duct enlargement and pancreatic edema. An abdominal CT scan was performed, showing extensive pancreatic edema, mesenteric edema, the presence of peripancreatic fluid and fluid in the pelvic space, and bilateral pleural effusion. A diagnosis of severe acute pancreatitis was made; there were no gallstones, biliary tree pathologies or structural abnormalities in the pancreas. The only significant factor in our search for a cause was that the patient had taken indomethacin over the past three weeks. APACHE II scores (33) and Ranson's criteria (7) were calculated. Blood gas analysis indicated metabolic acidosis (pH, 7.36; PaO₂, 56 mmHg; PaCO₂, 22.4 mmHg; HCO₃, 15.7 mEq/L; bas excess, -6.5). The patient was intubated and sedated using midazolam and fentanyl infusion for respiratory management. The patient was managed with supportive therapy, nasogastric suction, intravenous rehydration, hypercaloric parenteral nutrition and analgesic and antiprotease medications. Antibiotic therapy was added as well as insulin therapy for a persisting high glucose level (245 mg/dL, reference range: 75-115 mg/dL). Successively, his clinical condition slowly improved. The patient started to eat on the 32nd day after admission

with no episodes of vomiting or pain. Intravenous fluids and antibiotics were discontinued soon after. Mild pleural effusion was still present at CT scan, as well as slight pancreatic edema and massive peripancreatic fluids which subsequently decreased. The patient was discharged in apparently good physical condition. He was discharged on day 44 with instructions to avoid indomethacin in the future.

DISCUSSION

The proportion of cases of pancreatitis caused by drugs of all types is estimated to be about 2% in the general population [5]. Clear evidence of a definite association with pancreatitis, by means of rechallenge tests or consistent case reports supported by animal experiments or data on the acute incidence of pancreatitis in drug trials exists for didanosine, sodium valproate, amino-salicylates, estrogen, and calcium [5]. An association with drug-induced pancreatitis is likely, but not proven, for thiazide diuretics, ACE inhibitors, some NSAIDs, clozapine, interferon alfa-2b, and statins [6, 7]. Pancreatitis induced by the non-steroid anti-inflammatory agent, ketorolac, has been reported in the literature [8, 9]. Despite the low incidence of drug-induced pancreatitis, all patients with acute pancreatitis of an unknown etiology should be carefully questioned about drugs which could possibly be responsible for triggering the disease.

Drug-induced pancreatitis occurs rarely in clinical practice [10]. Proposed criteria for classifying drugs as having an association with pancreatitis [11] include the following: pancreatitis develops during treatment with the drug; other likely causes of pancreatitis are not present; pancreatitis resolves upon discontinuing the drug; pancreatitis usually recurs upon readministration of the drug. In our case, all other causes of pancreatitis were ruled out. There was no history of alcohol use and no family history of pancreatitis. There was no evidence of gallstone disease, and serum values of calcium and triglycerides were normal. The patient was not taking any

other medication. Our patient had been taking indomethacin for a few weeks before the onset of acute pancreatitis.

No data exists regarding a possible mechanism for indomethacin-induced pancreatitis. Oxidative stress plays an important role in the early stage of acute pancreatitis, as well as in associated multiple organ injury [12]. Heightened oxidative stress characterized by glutathione depletion may be of importance in mediating the progression from mild to severe pancreatitis [13]. Reactive oxygen species and lipid peroxidation play a role in the pathogenesis induced by the non-steroidal anti-inflammatory drug indomethacin [14]. In indomethacin-treated rats, cytosolic Cu/Zn superoxide dismutase and mitochondrial Mn-superoxide dismutase activities were significantly diminished in the gastric mucosa as were the total-superoxide dismutase activities in the testis. In addition, the glutathione content in both tissues was markedly decreased following indomethacin treatment [14]. The exact mechanism of indomethacin-induced pancreatitis is unknown. Indomethacin is possibly associated with decreased glutathione levels, decreased superoxide dismutase activities and increased oxidative stress.

In conclusion, we have described a case of indomethacin-induced pancreatitis. This is the first report in the literature regarding indomethacin-induced pancreatitis and it further reinforces the fact that NSAID may cause acute pancreatitis. Despite the low incidence of drug-induced pancreatitis, all patients with acute pancreatitis of an unknown etiology should be carefully questioned about drugs which could possibly be responsible for the induction of the disease. As the use of NSAID increases, physicians should consider the diagnosis of acute pancreatitis in patients taking these medications who then develop abdominal pain not explained by any other process. If pancreatitis is suspected, the drug should be stopped and substituted in order to reduce the possibility of further episodes of pancreatitis.

Received April 27th, 2005 - Accepted May 4th, 2005

Keywords Case Reports; Indomethacin; Pancreatitis, Acute Necrotizing

Correspondence

Dilek Memis
Trakya University Medical Faculty
Department of Anesthesiology and
Reanimation
22030, Edirne
Turkey
Phone: +90-284.235.7641/3039
Fax: +90-284.235.8096
E-mail: dilmemis@mynet.com

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