JOP. J Pancreas (Online) 2006; 7(3):321-323.

LETTER

Indomethacin-Induced Pancreatitis. A Second Case Report

Wassim Mahjoub, Slim Jarboui, Mounir Ben Moussa, Mohamed Morched Abdesselem, Abdeljelil Zaouche

General Surgery, Surgical Unit A, Hôpital Charles Nicolle. Tunis, Tunisia

Dear Sir:

We read about the case of indomethacin-induced pancreatitis reported by Memis *et al*. with great interest [1]. It seems to be the first report which attributed pancreatitis to Indomethacin intake despite the presence of small gallstones in the gallbladder.
We report herein a case of indomethacin-induced pancreatitis which is not associated with biliary gallstones. The aim of this letter is to discuss the modality of diagnosis and therapeutic consequences.

Case report

A 71-year-old woman presented to the Emergency Unit with a one-day history of severe epigastric pain of sudden onset with nausea and vomiting. Her medical history was significant for hypertension which had been treated by captopril for one year and rheumatoid arthritis treated by indomethacin for one month. There was neither history of alcohol consumption nor trauma. No family history of pancreatitis was noted. Her physical examination revealed a mildly distended abdomen with epigastric tenderness. Laboratory data showed elevated blood amylase (918 IU/L; reference range: 40-84 IU/L) and urine amylase levels (8,080 IU/L; reference range: 60-240 IU/L), an elevated white cell count (17,000 mL^{-1}; reference range: 4,000-10,000 mL^{-1}) and hypocalcemia (1.8 mmol/L; reference range: 2-2.25 mmol/L). Serum values of urea and creatinine were within normal reference levels. Bilirubinemia was 106 mmol/L (reference range: 5-17 mmol/L) and direct bilirubinemia was 5 mmol/L (reference range: 0-5 mmol/L). Alanine aminotransferase (27 IU/L reference range: 0-35 IU/L), lactate-dehydrogenase (320 IU/L reference range: 160-320 IU/L), gamma-glutamyltransferase (40 IU/L; reference range: 8-40 IU/L), and alkaline phosphatase (128 IU/L; reference range: 40-130 IU/L) were within the normal range. Cholesterol (4.20 mmol/L; reference range: 3.78-6.32 mmol/L) and triglycerides (0.86 mmol/L; reference range: 0.57-1.97 mmol/L) were normal.
A diagnosis of pancreatitis was made. The Ranson score was equal to three. Abdominal ultrasound revealed a normal biliary tree without any choledocholithiasis. The Wirsung duct was dilated with hypertrophy of the pancreas. Abdominal computed tomography (CT) showed diffuse pancreatic necrosis with fluid collections in the anterior lateral space of both kidneys and in the lower omental sac.
The course was uneventful with progressive clinical improvement; the patient started to eat one week after admission with no vomiting or pain. CT of the abdomen carried out on the 10^{th} day showed regression of the pancreatic and peripancreatic lesions.
Concerning the etiology of this severe pancreatitis, a second hepatic ultrasound failed to demonstrate any gallstones in the biliary tract. Lipid serum values were normal. There was neither history of trauma, family history of pancreatitis nor a viral syndrome in

the period prior to hospitalization. Captopril can cause pancreatitis, but our patient had taken it for one year and it was well-tolerated. The recent administration of indomethacin made us suspect its involvement in this severe acute pancreatitis. The patient was discharged from the hospital on day 15; she was apparently in good physical condition and was advised to avoid indomethacin.

Comment

Few data exist about the incidence of drug-induced pancreatitis in the general population. Drug intake is estimated to be involved in 1.4 to 2% of cases of pancreatitis [2, 3]. Despite this low incidence of drug-induced pancreatitis, all patients with acute pancreatitis should be carefully questioned about drug intake. Pancreatitis is often ignored as a side-effect of drugs since it is difficult to establish the cause-effect relationship. Three criteria are needed for a drug to be considered a causative factor of pancreatitis: the development of pancreatitis during treatment with this drug, the resolution of the pancreatitis upon discontinuing the drug and pancreatitis recurrence after re-administration of the drug [4].

Drugs suspected of generating acute pancreatitis are classified into three classes: Class I, including medications implicated in more than 20 reported cases with at least one documented case following re-exposure (asparaginase, azathioprine, tetracyclines, etc.); Class II, comprising medications implicated in more than 10 cases (rifampin, Octeroitid, Carbamazipine, etc.); Class III, comprising all other medications reported in the literature [5]. Indomethacin is included in the third class.

The physiopathology of indomethacin-induced pancreatitis has not yet been elucidated but, as suggested by Memis *et al*. [1], it probably implicates a decrease in glutathione levels, a decrease in superoxide activities and increased oxidative stress.

In our patient, two abdominal ultrasonographies ruled out a biliary origin. However, in the case reported by Memis *et al*. [1], abdominal ultrasonography revealed small gallstones in the gallbladder, therefore suggesting the necessity of doing a cholecystectomy. Our patient did not have a history of alcohol intake, recent abdominal trauma or viral syndromes preceding her admission into our Department. Biological testing for viral infections was not performed.

In conclusion, due to the coincidence in time between the recent introduction of indomethacin and the occurrence of the acute pancreatitis, and the exclusion of other possible etiological factors, the diagnosis of necrotizing pancreatitis induced by indomethacin was made.

Conclusion

Considering the increased use of non-steroid anti-inflammatory drugs, physicians should consider the diagnosis of acute pancreatitis in patients taking these medications, and irrespective of the mechanism of indomethacin-induced pancreatitis, the message here is that indomethacin should be permanently avoided once it has been documented as causing acute pancreatitis.

Received February 19th, 2006 - Accepted February 21st, 2006

Keywords Anti-Inflammatory Agents, Non-Steroidal; Case Reports; Indomethacin /adverse effects; Pancreatitis, Acute Necrotizing

Correspondence
Wassim Mahjoub
General Surgery, Surgical Unit A
Hôpital Charles Nicolle
1006 Tunis
Tunisia
Phone: +216-9826.8943
Fax: +216-7135.4364
E-mail: wassim_mahjoub2002@yahoo.fr

References

1. Memis D, Akalin E, Yucel T. Indomethacin-Induced Pancreatitis: A Case Report. JOP. J Pancreas (Online) 2005; 6:344-7. [PMID 16006685]

2. Andersen V, Sonne J, Andersen M. Spontaneous reports on drug-induced pancreatitis in Denmark from1968 to 1999. Eur J Clin Pharmacol 2001; 57:517-21. [PMID 11699619]

3. Anagnostopoulos GK, Tsiakos S, Margantinis G, Kostopoulos P, Arvanitidis D. Acute pancreatitis due to pravastatin therapy. JOP. J Pancreas (Online) 2003; 4:129-32. [PMID 12743419]

4. Mallory A, Kern F Jr. Drug-induced pancreatitis: a critical review. Gastroenterology 1980; 78:813-20. [PMID 6986321]

5. Trivedi CD, Pitchumoni CS. Drug-induced pancreatitis: an update. J Clin Gastroenterol 2005; 39:709-16. [PMID 16082282]

REPLY

Dear Sir:

I read about the case of indomethacin-induced pancreatitis reported by Mahjoub *et al*. with great interest [1]. Mahjoub's research together with my reports dealing with pancreatitis caused by indomethacin are in the literature and they further reinforce 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 cause. If pancreatitis is suspected, the drug should be stopped and replaced to reduce the possibility of further episodes of pancreatitis.

Dilek Memis

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

Received February 24th, 2006

Keywords Anti-Inflammatory Agents, Non-Steroidal; Comment; Indomethacin /adverse effects; 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

References

1. Mahjoub W, Jarboui S, Ben Moussa M, Abdesselem MM, Zaouche A. Indomethacin-induced pancreatitis: a second case report. JOP. J Pancreas (Online) 2006; 7:321-323.