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Diclofenac Induced Pancreatitis: A Case Report

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ABSTRACT

We report a case of a 30-year-old male presented with acute pancreatitis after a period of diclofenac (Voltaren®) use. Other causes of pancreatitis were ruled out by thorough history, physical examination and investigations. The patient was admitted and treated conservatively for five days and made a full recovery after the diclofenac was discontinued. To our knowledge, and as reported previously, it appears that diclofenac happens to be the only logical cause for this event. However, further evidence and studies are required to prove the association versus causative relation between usage of diclofenac and pancreatic insult.

Keywords

Pancreatitis, Diclofenac, Drug induced, Voltaren, NSAID, Case report

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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]. A variety of drugs have been associated with acute pancreatitis such as thiazide diuretics, furosemide, azathioprine, tetracycline, zidovudine, fibrates, estrogen-containing oral contraceptives and overdose with acetaminophen. Less conclusive evidence exists for corticosteroids, chlorthalidone, ethacrynic acid, phenformin and procainamide[3–5].

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) taken as an anti-inflammatory, antipyretic and analgesic, which is thought to exert its effect through blocking of prostaglandin synthesis by inhibition of cyclo-oxygenase (COX). It also appears to exhibit bacteriostatic activity by inhibiting bacterial DNA synthesis[6]. It is the most potent NSAID on a broad basis[7].

Although pancreatitis is a very rare adverse effect of diclofenac, yet a few cases of diclofenac-induced pancreatitis have been reported in the literature[8].

CASE REPORT

A 30-years-old male patient working at an airline company, not known to have any medical illness, presented to the Emergency Room (ER) in his local vicinity with the complaint of a tooth ache, which was managed by giving him a dose of 50 mg diclofenac intramuscular (IM) injection and a prescription of oral diclofenac, after that he was discharged home to follow-up later with a dentist. The patient received the IM injection diclofenac at 8:00 p.m., then when at home, he took another dose of 50 mg orally at about 12:00 a.m. midnight. Next morning, the patient started to have abdominal pain, the pain was sudden in onset and gradually increasing in severity, located mainly in the epigastric region, and radiating directly through the abdomen to the back. The pain was aggravated by lying flat on his back and partially improved by leaning forward. There was a history of vomiting twice, once at home and the other in the ER, the vomitus contained bile and food but no blood. There was no history of alcohol or drug ingestion other than the previously mentioned diclofenac. There was no history of trauma, hypertriglyceridemia, cholelithiasis or other medical causes of pancreatitis.

TABLE 1.
List of initial blood works on presenting to emergency department.

Test	Result	Unit	Normal Range
Total Bilirubin	0.6	mg/dl	(up to 1.0)
Direct Bilirubin	0.2	mg/dl	(up to 0.3)
Alkaline Phosphatase [ALP]	75	U/L	(50 - 136)
Alanine Transaminase [ALT]	98*	U/L	(30 - 65)
Aspartate Transaminase [AST]	124*	U/L	(15 - 37)
Gama-glutamyl Transferase [GGT]	189*	U/L	(5 - 85)
Total Protein	6.9	g/dl	(6.4 - 8.2)
Albumin	4.1	g/dl	(3.4 - 5)
Triglycerides	62	mg/dl	(30 - 150)
Blood Urea Nitrogen [BUN]	10	mg/dl	(7 - 18)
Creatinine	0.8	mg/dl	(0.6 - 1.3)
Amylase	2268*	U/L	(25 - 115)
Serum Lipase	19079*	U/L	(114 - 286)
Hemoglobin	15.5	g/dl	(13.5-17.5)
White Blood Cell Count [WBC]	$11x10^9$	/L	$(4-11)x10^9$
Prothrombin Time [PT]	19	seconds	(12 – 16)
Glucose	5.3	mmol/L	(4.4 – 6.6)
Calcium	2.30	mmol/L	(2.20 – 2.67)
Sodium	140	mmol/L	(135 – 146)
Potassium	4.2	mmol/L	(3.5 – 5)
Bicarbonate	20	mmol/L	(22 – 26)

**Abnormal results*

No history of surgery or endoscopic retrograde cholangiopancreatography (ERCP). His family history was negative for dyslipidemia, cholelithiasis and pancreatitis. Systemic review was unremarkable.

On physical examination the patient was conscious and oriented, he was vitally stable with blood pressure of 110/60 mmHg and no postural drop, heart rate of 96 beats/min, temperature of 37.4°C, respiratory rate of 16/min. Abdominal examination revealed epigastric tenderness without any mass or organomegelay. Chest and cardiovascular systems were normal.

INVESTIGATIONS

Initial blood works on presenting to ER are listed in (Table 1).

MANAGEMENT COURSE SINCE ADMISSION TILL DISCHARGE

Patient was admitted as a case of acute pancreatitis for further investigation and management.

Ultrasound showed normal homogenous echo pattern of the liver parenchyma with no focal hepatic lesions. No intrahepatic biliary radicles dilatation. Common bile duct (CBD) was within normal calibers. Gall bladder was of normal size, shape and wall thickness with no calculi or sludge inside. Spleen and both kidneys appeared normal. Pancreas was masked by bowel gases making it difficult to be assessed. No ascites.

Abdomen computer tomography (CT) scan was done and showed edematous pancreas but no necrosis, consistent with mild to moderate pancreatitis. The patient was managed conservatively by keeping him nil per oral (NPO) on intravenous fluids (IVF) and pain control on Tramadol 50 mg PO TID for 72 hrs then switched to PRN. On the 3rd day clear fluid diet was started and well tolerated so by day 4, IVF was discontinued and patient was tolerating oral feeding, and by the 5th day patient was able to tolerate full diet. He also received a course of antibiotic for his dental problem.

Enzymes were closely monitored, which showed marked improvement on stopping the offending drug, along with the conservative treatment.

Figures 1-3 shows the marked improvement in pancreatic and hepatic enzymes after stopping the offending drug.

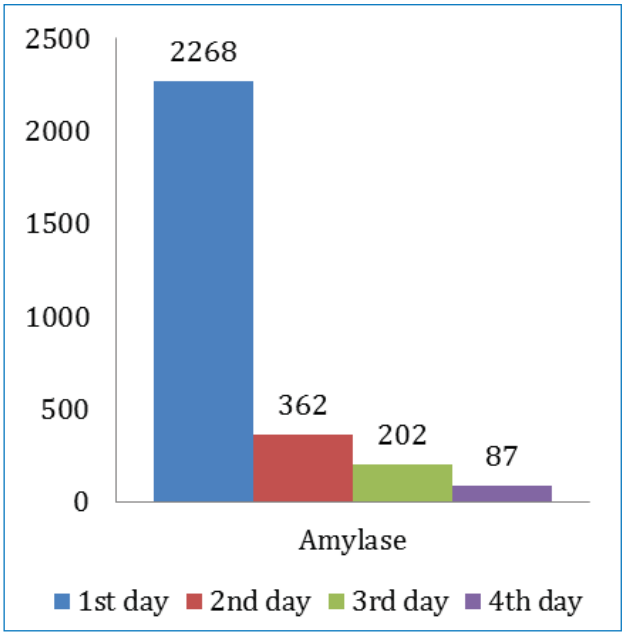

FIGURE 1.
Shows the marked improvement in the Amylase enzyme level after stopping the offending drug.

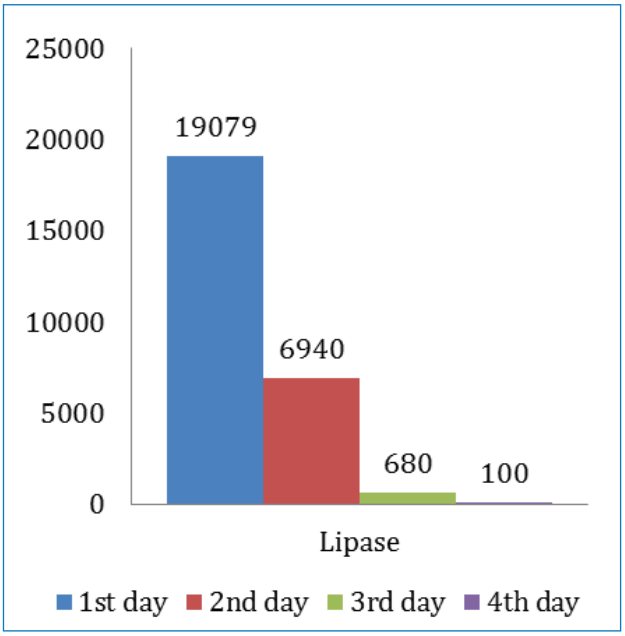

FIGURE 2.
Shows the marked improvement in the Lipase enzyme level after stopping the offending drug.

DISCUSSION

The proportion of cases of pancreatitis caused by drugs of all types is estimated to be about 2% in the general population[9]. Clear evidence of a definite association with pancreatitis by means of re-challenge 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, aminosalicylates, estrogen, and calcium[9]. An association with drug-induced pancreatitis is likely, but not proven, for thiazide diuretics, ACE inhibitors, some NSAIDs, clozapine, interferon alfa-2b, and statins[10,11]. Pancreatitis induced by NSAIDS, ketorolac has been reported in the literature[12,13]. Despite the low incidence of drug-induced pancreatitis, high suspicion for it has to be considered by physicians assessing patients with acute pancreatitis, especially when the etiology is ambiguous, Table 2 shows a list of similar cases from the literature of pancreatitis all induced or thought to be induced by NSAIDs.

The proposed criteria for classifying the pancreatitis as drug-induced consists of the following: pancreatitis

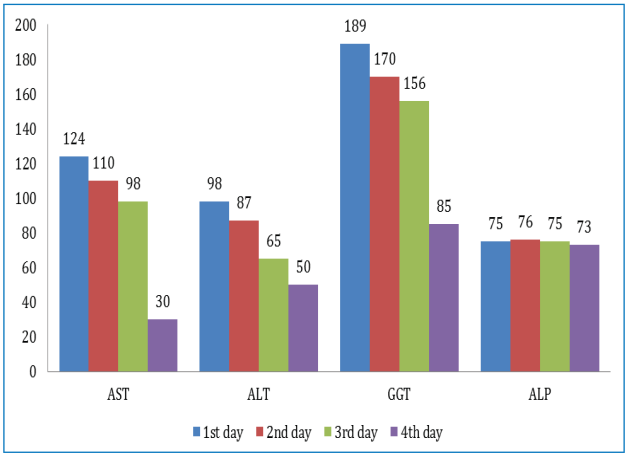

FIGURE 3.
Shows the marked improvement in the hepatic enzymes after stopping the offending drug (AST: aspartate transaminase, ALT: alanine transaminase, GGT: gama-glutamyl transferase, ALP: alkaline phosphatase).

develops during treatment with the drug; other likely causes of pancreatitis are not present; pancreatitis resolves upon discontinuing the drug; pancreatitis usually recurs upon re-administration of the drug[14]. Our patient certainly met at least three of these criteria. He was not taking any medication at the time other than diclofenac. Other causes for both endogenous and iatrogenic pancreatitis has been objectively ruled out by thorough history and meticulous investigation. And finally, pancreatitis resolved upon stopping the offending drug. The forth criteria of provoking the insult by re-introducing the offending drug was not ethically valid in this case.

The mechanism of drug-induced pancreatitis is not well established. Allergic reactions, free radical toxicity, and an increased susceptibility to infections has been suggested as possible pathogenic mechanisms[15]. A study by Standfield and Kakkar (1983)[16] examined the interesting hypothesis that a cytoprotective benefit of prostaglandins similar to that seen in the gastrointestinal mucosa may also exist in pancreatic cells. Improved survival was demonstrated in a mouse model of experimental pancreatitis after subcutaneous administration of prostaglandin E2, compared with 100% mortality in control animals that were not treated with prostaglandins. In contrast, administration of aprotinin did not improve survival. The authors speculated that prostaglandins exerted a membrane stabilizing effect in pancreatic cells and demonstrated a reduction in blood concentration of markers of membrane instability in twelve human cases of pancreatitis following prostaglandin administration. These results suggest that prostaglandin inhibition may be a possible mechanism of NSAID-induced acute pancreatitis and further studies with prostaglandin analogues such as misoprostol could be designed to investigate this hypothesis.

As in our case, it is likely that NSAIDs can induce pancreatitis. For this particular reason, side effects such as vomiting and abdominal pain should not only be directly related to common conditions such as gastritis, or peptic ulceration, but also to rare and serious conditions such as pancreatitis. Therefore, it it is suggested that measuring amylase level in patients using NSAIDs who present

TABLE 2.
List of NSAID induced pancratitis cases that were published throughout the literature.

Year of Publication	Name of the Drug	No. of Cases
2013[17]	Aspirin	1
2012[18]	Aspirin	3
2007[19]	Celecoxib	1
2006[20]	Naproxen	1
2006[21]	Rofecoxib	1
2006[22]	Ibuprofen	1
2006[23]	Piroxicam	1
2006[24]	Indomethacin	1
2005[25]	Indomethacin	1
2002[26]	Celecoxib	1
2002[12]	Ketorolac tromethamine	1
2002[27]	Rofecoxib	1
2001[28]	Ketoprofen	1
2000[29]	Celecoxib	1
2000[30]	Celecoxib	1
1998[31]	Ketoprofen	1
1998[32]	Ketoprofen	1
1998[13]	Ketorolac tromethamine	1
1995[33]	Naproxen	1
1993[8]	Diclofenac	1
1993[34]	Piroxicam	1
1993[35]	Naproxen	1
1992[36]	Sulindac	1
1992[37]	Sulindac	2
1992[38]	Ketoprofen	1
1989[39]	Sulindac	2
1987[40]	Sulindac	1
1986[41]	Piroxicam	1
1986[42]	Sulindac	1
1985[43]	Oxyphenbutazone	1
1983[44]	Sulindac	1
1982[45]	Oxyphenbutazone	1
1982[46]	Sulindac	1
1982[47]	Mefenamic acid	1
1981[48]	Sulindac	1
1981[49]	Salicylate	1
1980[50]	Sulindac	1
1980[51]	Sulindac	1
1967[52]	Indomethacin	1

with such symptoms, may be a wise practice to detect pancreatitis at an early stage and manage it to prevent complications.

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التهاب البنكرياس المستحث بالديكلوفيناك: حالة تقريرية

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المستخلص:

هذا التقرير عن حالة ذكر يبلغ من العمر ٣٠ عامًا قدم بالتهاب البنكرياس الحاد بعد فترة من استخدام الديكلوفيناك (فولتارين®). تم استبعاد اي أسباب اخرى للإلتهاب البنكرياسي بعد أخذ تاريخه المرضي والفحص البدني المفصل والتحاليل والأشعات الشاملة. بناء على ذلك، تم تنويم المريض وعلاجه لمدة خمسة أيام بدون اي تدخل دوائي، ولوحظ شفاء المريض التام بعد التوقف عن استعمال الديكلوفيناك. على حد علمنا، وكما ذكر من قبل، يبدو أن استعمال الديكلوفيناك هوا السبب المنطقي الوحيد لهذا الحدث، وهناك حاجة لمزيد من الادلة والدراسات لإثبات الرابط السببي بين استخدام الديكلوفيناك وإلتهاب البنكرياس الحاد.