

Pancreatitis associated with diclofenac

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Summary: A 34 year old female developed acute pancreatitis after commencing diclofenac for a painful arthropathy. The possible role of prostaglandin inhibition in non-steroidal analgesic drug-induced pancreatitis is discussed and the suggestion is made that serum amylase should be measured in patients who develop abdominal pain, following ingestion of non-steroidal anti-inflammatory drugs.

Introduction

A variety of drugs have been associated with acute pancreatitis such as thiazide diuretics, frusemide, azathioprine, tetracycline, zidovudine, fibrates, oestrogen-containing oral contraceptives and overdose with acetaminophen. Less conclusive evidence exists for corticosteroids, chlorthalidone, ethacrynic acid, phenformin and procainamide.^{1–3} We describe a case of acute pancreatitis following the use of diclofenac.

Case report

A 34 year old housewife presented with a painful arthropathy affecting the fingers. Two years previously, while residing in Germany, investigations for painful finger arthropathy revealed a weakly positive rheumatoid factor and negative anti-nuclear and anti-DNA antibodies. She had no past history of alcohol misuse, hyperlipidaemia, diabetes, renal disease or gallbladder disease and was on no medication. Diclofenac 50 mg (Voltarol, Geigy) three times daily was prescribed. In addition to diclofenac she took two capsules of a combination of paracetamol 500 mg and codeine 30 mg (Tylex, Cilag) 9 and 10 days later. She had never used diclofenac previously but had taken paracetamol and codeine in the past with no ill effects.

On the tenth day she developed nausea and vomiting which continued despite stopping the paracetamol and codeine combination. Diclofenac was stopped and 2 days later she was admitted with

vomiting and severe abdominal pain radiating to the back. On examination she was afebrile with a heart rate of 90/minute and a blood pressure of 100/60 mmHg. Abdominal examination revealed epigastric tenderness and absent bowel sounds.

Laboratory investigations were as follows: haemoglobin 141 g/l, white cell count $14.1 \times 10^9/l$, platelets $370 \times 10^9/l$. Serum urea 17.5 mmol/l, creatinine 274 $\mu\text{mol/l}$, glucose 5.3 mmol/l, amylase 811 U/l (normal < 340 U/l), calcium 1.92 mmol/l, albumin 35 g/l, total protein 78 g/l, potassium 2.2 mmol/l, bicarbonate 9 mmol/l, sodium 138 mmol/l. Liver function tests were normal. Serum cholesterol concentration was 4.4 mmol/l and triglyceride 0.9 mmol/l. Prothrombin time was 19 seconds (control 14 seconds). Serum complement assay, ASO titres, blood cultures and urine cultures were normal as was serology for mumps, coxiella, adenovirus, influenza virus, hepatitis virus, chlamydia, salmonella and respiratory syncytial virus. Rheumatoid factor, anti-nuclear antibodies and anti-DNA antibody assay were negative. Abdominal ultrasound examination revealed a normal sized liver and spleen, absence of gallstones and a normal sized common bile duct. The pancreas was oedematous and there was no free fluid in the abdomen. The kidneys were of normal size and there was no urinary obstruction.

She was treated with intravenous fluids, replacement of electrolytes and nasogastric suction. Serum amylase concentration peaked to 5,159 U/l 10 days after the onset of the abdominal symptoms and serum creatinine rose to 304 $\mu\text{mol/l}$. Her symptoms improved over the ensuing days and she was discharged 12 days after admission. Two months later she was asymptomatic with serum creatinine 171 $\mu\text{mol/l}$, amylase 233 U/l, calcium 2.09 mmol/l, albumin 37 g/l and bicarbonate 19 mmol/l.

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Discussion

Drugs associated with pancreatitis have been classified into three groups.⁴ In the first group the association is regarded as definite and fulfils the criteria of pancreatitis developing during treatment with the drug, disappearing upon drug withdrawal and, recurring again when the drug is reintroduced. In the second category a probable association is thought to exist when some but not all the above conditions are fulfilled; the third group contains drugs which have been proposed as causes of pancreatitis, but the published evidence is either inadequate or contradictory.

Acute pancreatitis in the patient described was probably due to diclofenac consumption. Symptoms developed 11 days after commencing the drug and there were no known predisposing causes of pancreatitis such as alcohol misuse, hypercalcaemia, hyperlipidaemia or gallbladder disease. A definite causative association could only have been established after rechallenging the patient with the drug. Deliberate subjection of a patient to a potentially serious or lethal disease can be ethically justified only if the drug in question—and only that drug—is essential for treatment of a serious illness.⁴ The ingestion of two capsules of a combination of paracetamol and codeine was unlikely to be a cause of her pancreatitis as the patient had used both these drugs in the past without any ill effects.

Two months following her admission our patient had residual renal impairment with a serum creatinine concentration of 171 $\mu\text{mol/l}$. Unfortunately a serum creatinine concentration prior to her current illness was not available. It is possible that she also suffered from non-steroidal induced interstitial nephritis or that she had mild renal impairment predating her current illness.

Only eight cases of pancreatitis associated with non-steroidal anti-inflammatory drugs (NSAIDs) have been published before; five were associated with sulindac and one each with indomethacin, piroxicam and mefenamic acid.⁵⁻⁷ To our

knowledge there have been no previously published cases of pancreatitis following diclofenac ingestion. An inquiry to the Committee for Safety of Medicines, however, revealed that during the past 8 years one case of acute pancreatitis following diclofenac ingestion had been reported to the Committee. The mechanism of drug-induced pancreatitis is not established. Allergic reactions, free radical toxicity, and an increased susceptibility to infections have been suggested as possible pathogenic mechanisms.⁸ A recent study⁹ has examined the interesting hypothesis that a 'cyto-protective' 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 who were not treated with prostaglandins. In contrast administration of aprotinin did not improve survival. The authors speculate that prostaglandins exert a membrane stabilizing effect in pancreatic cells and demonstrated a reduction in blood concentration of markers of membrane instability in 12 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.

Very few cases of pancreatitis associated with NSAIDs have been reported. It is possible that subacute pancreatitis may not be recognized because patients with less severe symptoms are not tested routinely for raised serum amylase. Abdominal pain, vomiting and nausea are often reported by patients using NSAIDs and these symptoms may be regarded as manifestations of gastritis, or peptic ulceration. We suggest that patients who report such symptoms while on NSAID therapy should be tested for a raised serum amylase to exclude pancreatitis.

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