

A Case of Sulindac-induced Enteropathy Resulting in Jejunal Perforation

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for rheumatic conditions. Their effects on the upper gastrointestinal tract are well recognised. Clinically important damage to the small intestines is less common and often unrecognised. We report a case of sulindac-induced jejunal perforation in a rheumatoid arthritis (RA) patient with previous gastrectomy for gastric carcinoma. The prevalence, diagnosis, pathogenesis and treatment options of NSAID-induced enteropathy will be discussed.

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of various rheumatic conditions including rheumatoid arthritis (RA). The adverse effects of NSAIDs on the upper gastrointestinal tract (GIT) are well known and well described. They cause mucosal damage to the upper GIT, including an increased incidence of gastric and duodenal ulcers.¹ During the past decade, clinically important damage by NSAIDs beyond the duodenum has been recognised,² e.g. ulceration and stricture. We describe a case of jejunal ulceration and perforation due to sulindac in a RA patient with previous gastrectomy. We also review the literature on NSAID-induced enteropathy including the pathogenesis and treatment options.

Case Report

LCH, a 60-year-old Chinese male presented to the medical clinic at Alexandra Hospital in September 1991 with a one-month history of morning stiffness and symmetrical polyarthritis. There were no extra-articular features.

Investigations showed a high titre of rheumatoid factor 2560 in/ml. LCH was diagnosed to have active seropositive RA, and was started on prednisolone, D-penicillamine, and ketoprofen. He developed epigastric pain after taking ketoprofen which was subsequently discontinued. A barium meal done in October 1991 was normal. Low dose mefenamic acid (with cimetidine) was substituted for the control of arthritic pain. However, he continued to have recurrent epigastric pain.

Oesophageal-gastroduodenoscopy in November 1991 showed multiple gastric and duodenal ulcers. Mefenamic acid and D-penicillamine were stopped and omeprazole was given. The gastric biopsy was later reported to show moderately differentiated adenocarcinoma. The patient underwent a subtotal gastrectomy and gastrojejunostomy in December 1991. Histology confirmed the presence of early gastric carcinoma and the resection margins were free of tumour. A follow-up computed tomographic (CT) scan of the abdomen did not show any liver secondaries. The RA was controlled with prednisolone and D-penicillamine was restarted in February 1992.

In September 1992, he suffered a flare of his arthritis and his therapy was changed. He finally responded to a combination of analgesic (Tramadol), prednisolone, azathioprine and sulindac. He developed mild steroid-induced diabetes mellitus. He remained well on this treatment regime and in September 1993 methotrexate was substituted for azathioprine. He underwent arthroscopic synovectomy of his right knee and total right hip replacement. His medications were unchanged for a few years and he was fairly well.

In September 1996, he complained of giddiness, visual blurring and malaena of one-week duration. He was found to have iron-deficient anaemia with a haemoglobin of 10.2 g/dl and was extensively investigated. Oesophagogastrroduodenoscopy (OGD) done was normal. Colonoscopy showed malaena until the caecum. CT scan of the abdomen was normal. A small bowel series showed Bilroth II gastrectomy with good flow of barium through the anastomosis with normal remnant

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stomach, small bowel and terminal ileum. The bleeding stopped and he was continued on his usual medication (including sulindac) for his arthritic pain.

In January 1997, the patient was hospitalised with an acute abdomen. His blood counts showed haemoglobin of 14.3 g/dl, total white cell count of 8590/mm³, platelet count of 372 x 10⁹/L, erythrocyte sedimentation rate (ESR) of 76 mm/h. Urea, electrolytes, amylase were normal. Chest X-ray did not show any air under the diaphragm. Abdominal X-ray showed distended small bowel loops. CT scan of the abdomen showed free-air and fluid in the peritoneum, and dilated loops of bowel suspicious of bowel perforation (Fig. 1). Emergency laparotomy revealed loops of jejunum adherent to the anterior abdominal wall with a small perforation just proximal to the adherent portion. Moderate soiling of the peritoneal cavity was noted. Histology confirmed the presence of a perforated jejunal ulcer, with no evidence of malignancy or vasculitis. The postoperative recovery was uneventful and the NSAID was discontinued. His RA is presently controlled with prednisolone, methotrexate and sulphasalazine and Tramadol when necessary.

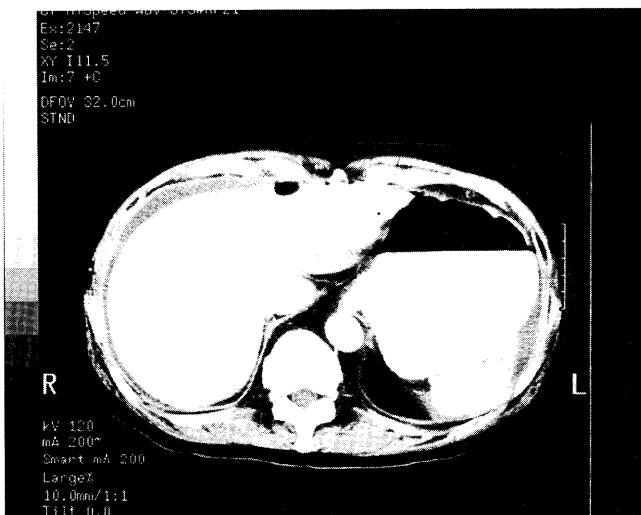


Fig. 1. CT scan of abdomen showing free air in the peritoneum.

Discussion

Although the incidence of NSAID-induced gastrointestinal complications is relatively low,¹ the vast number of patients exposed to NSAIDs amounts to a considerable clinical problem. In the RA population in the USA, an estimated 20 000 hospitalisations and 2600 deaths per year are attributable to NSAID-related gut toxicity.⁷ Whereas clinicians are well aware of the effects of NSAIDs on the upper GIT, the entity of NSAID-induced enteropathy is often not recognised.

Small intestinal perforation is an uncommon compli-

cation of NSAIDs.² Other adverse effects of NSAIDs on the small bowel include massive bleeding, strictures (diaphragm-like or broad-base), unexplained iron-deficiency anaemia, protein loss, ileal dysfunction and malabsorption of fat and xylose.

Forty-six cases of NSAID-induced enteropathy have been described in the English literature.^{3,4} These patients were taking a variety of NSAIDs including indomethacin, piroxicam, naproxen for various inflammatory conditions such as RA. The duration of NSAID use was usually greater than one year, though five cases have been described after use of medication for less than four weeks. Of these 46 patients, 10 had intestinal obstruction, 10 had ulceration and anaemia, 3 had intestinal perforation, 21 had unexplained iron-deficiency anaemia, and 2 had villous atrophy. There was one case report of diarrhoea and villous atrophy due to sulindac.⁵ This is the first reported case of sulindac-induced jejunal perforation in a patient with RA.

How common is NSAID-induced enteropathy? The prevalence and morphologic features of jejunal and ileal mucosal lesions in an autopsy of 713 consecutive patients with and without NSAID use was studied by Allison and colleagues.⁶ Non-specific small intestinal ulcers were found in 8.4% of NSAIDs users versus 0.6% in control subjects. The prevalence of these lesions was lower than that of gastric and duodenal ulcers, which were 21.7% and 12.3%, respectively. Long-term users of NSAIDs (> 6 months) were at a higher risk of developing intestinal lesions (14%). In addition, 3 patients who had received long-term NSAIDs died of undiagnosed small bowel perforation.

Bjarnason and colleagues⁷ studied 97 patients with RA and osteoarthritis who had been taking NSAIDs for more than 2 months. Using indium scintiscans and a 4-day quantitative faecal collection of indium, they found that two-thirds of the patients had intestinal inflammation. This 66% prevalence rate of indium scan diagnosis of enteropathy contrast with the 8.4% prevalence rate reported by Allison. This difference could be due to lack of specificity of the radionuclide scanning.

The diagnosis of NSAID-induced enteropathy can sometimes be made through the following investigations—small bowel barium studies, radionuclide scanning and small bowel enteroscopy.³ A small bowel barium study may show strictures, diaphragms, and focal areas of dilatation. A normal finding does not rule out the diagnosis of NSAID-induced enteropathy. Radionuclide tests have been used—indium scintiscans of the abdomen may be used to localise areas of inflammation, ⁵¹Cr-labelled ethylenediaminetetraacetic acid and ⁵¹Cr-labelled red blood cell scan have also been used to quantify intestinal permeability and intestinal blood loss respectively. However, these techniques have limited clinical utility due to cost, technical difficulty, and

the lack of studies on the sensitivity and specificity of the scan technique to diagnose NSAID-induced enteropathy. Small bowel enteroscopy has been used to detect intestinal blood loss in patients receiving NSAIDs. Direct visualisation of the small bowel mucosal and the ability to obtain biopsy tissue for histopathological confirmation are the main advantages. But the main disadvantages are that of limited technical expertise and up to 6 hours may be needed for the whole procedure. Through this technique, small intestinal mucosal abnormalities including erosions, frank ulcers, villous atrophy and red spots (early mucosal lesions) were identified.³

One have to bear in mind that besides NSAIDs, there are other causes of non-specific erosions and ulcerations of the small intestines. These include Crohn's disease, infection (cytomegalovirus, tuberculosis and yersinia), vasculitis (lupus and rheumatoid), and ischaemia. Rheumatoid vasculitis causing bowel infarction, ulceration, perforation, stricture and bleeding have variously been reported.^{8,9}

The pathogenesis of NSAID-induced enteropathy involves several factors, including impaired epithelial barrier function, decrease in systemic tolerance to luminal antigen,¹⁰ bile, luminal bacteria, and enterohepatic circulation of the NSAID.¹¹ It has been suggested that NSAID inhibition of cyclooxygenase 1 (COX 1) may be relatively unimportant in the pathogenesis of NSAID-induced enteropathy.¹⁰ This conclusion was based on animal studies where potent inhibitors of COX 1 like aspirin and nitrofenac did not cause small intestinal damage. NSAIDs appear to cause specific damage to enterocyte mitochondria during absorption by uncoupling oxidative phosphorylation.² This leads to reduced ATPase levels which result in loss of control of the integrity of the intercellular junction with increased intestinal permeability. Hence, the mucosal is exposed to luminal aggravating factors-bile, proteolytic enzyme, bacteria degradation products and finally a bacteria invasion of the mucosal. The neutrophils become attracted to the bacteria and release lysosomal enzymes leading to macroscopic damage with bleeding and protein loss.

Recent studies have also shown that the enterohepatic circulation of a NSAID is important in causing small intestinal damage.¹⁰ A direct correlation exists between the concentration of NSAID in the bile and the degree of small intestinal damage. Among the NSAIDs, indomethacin and piroxicam have the highest bile concentration. Pro-NSAIDs (nebumetone and sulindac) whose active metabolites are produced in the liver following absorption, do not undergo enterohepatic circulation and therefore do not increase permeability.

Interestingly, our patient who was on sulindac developed jejunal perforation, suggesting that other factors are involved in the pathogenesis of NSAID-induced

enteropathy besides enterohepatic circulation. Other mechanisms of NSAID-induced enteropathy include NSAID inhibition of anti-thrombotic eicosanoids and inducing pro-coagulant activity leading to intestinal microvascular injury and thrombosis.¹²

Recognising the cause of the enteropathy and discontinuing the use of the offending agent are the mainstay of treatment.³ In patients with villous atrophy due to NSAIDs, such measures may suffice. Prevention of NSAID-induced enteropathy is currently not possible. Misoprostol, unlike its use in the prevention of NSAID gastropathy, is not helpful in prevention of NSAID enteropathy. However, high doses of misoprostol have been shown to improve the anaemia in patients with proven NSAID-induced enteropathy.⁴

A more promising approach may be to produce newer NSAIDs which do not cause small intestinal damage. Nitrofenac, which is structurally similar to its parent compound diclofenac except for an attached nitric oxide moiety, is one such NSAID.¹⁰ It has equivalent anti-inflammatory and anti-pyretic activities but does not cause small intestinal damage in animal studies. Another NSAID with similar small intestinal sparing effects that has been reported in animal studies is nitroxybutyl-flurbiprofen.¹³ Fairly selective inhibitors of COX 2 (etodolac and nebumetone) have been shown to cause less small intestinal damage. However, this lack of damage may be more attributable to the lack of enterohepatic circulation of these compounds than to their selectivity for COX 2.¹⁰

Sulphasalazine has been used in the treatment of NSAID-induced enteropathy.³ There was a moderate but significant reduction in intestinal inflammation and intestinal blood loss when sulphasalazine was used in combination with sulcrafate and misoprostol. The role of sulphasalazine in the treatment of NSAID-induced enteropathy deserves further study. Based on the possibility that bacterial infection has a role as a neutrophil chemoattractant, metronidazole (800 mg/d) has been used as treatment in NSAID-induced enteropathy. Intestinal inflammation and blood loss were significantly reduced. Fifty per cent of patients had normal examination of ¹¹¹In following treatment.*

Intestinal obstruction is the most common indication for surgical treatment of NSAID-induced enteropathy. Occasionally, intestinal bleeding and perforation may necessitate surgical exploration, as shown in our patient.

Conclusion

NSAIDs are useful anti-rheumatic drugs and their use will continue to be widespread. NSAID-induced enteropathy, though less common than upper gastrointestinal side-effects, may have serious adverse consequences. Virtually all classes of NSAIDs have been implicated in

causing enteropathy with erosions, ulceration, bleeding and strictures. The pathogenesis is multifactorial. Diagnosis of NSAID-induced enteropathy is difficult. The therapeutic options include metronidazole, sulphasalazine and misoprostol. Clinicians prescribing NSAIDs to patients should be aware of the entity of NSAID-induced enteropathy.

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