

NON-STEROIDAL ANTI-INFLAMMATORY DRUG INDUCED INJURY TO THE SMALL INTESTINE

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Summary: Non-steroidal anti-inflammatory drug (NSAIDs) induced enteropathy represents an important complication of one of the most commonly used drugs worldwide. Due to previous diagnostics difficulties the real prevalence of this disease was underestimated for a long time. The pathogenesis of NSAID-enteropathy is more multifactorial and complex than formerly assumed but has still not been fully uncovered. A combination of the local and systemic effect plays an important role in pathogenesis. Thanks to novel enteroscopy methods (wireless capsule endoscopy, double balloon enteroscopy), small bowel lesions are described in a substantial section of NSAID users although most are clinically asymptomatic. The other non-invasive tests (small bowel permeability, faecal calprotectin, scintigraphy using faecal excretion of ¹¹¹indium-labelled leukocytes etc.) proposed for diagnostics are not generally used in clinical practice, mainly because of their non-specificity. Despite intensive research into possible treatment, the main measure for patients with NSAID-enteropathy is still withdrawal of NSAIDs. Double balloon enteroscopy plays an important role in the treatment of complications (bleeding, strictures).

Key words: *Non-steroidal Anti-inflammatory Drugs; Enteropathy; Gastrointestinal Endoscopy; Enteroscopy; Intestinal diseases*

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) represent the group of most commonly used drugs worldwide. The target group for use of NSAIDs comprises the elderly population with higher morbidity and mortality and a higher risk of drug toxicity (91). This fact together with the aging of the population in developed countries means increasing medical and economical problems in this context. In a large prospective analysis of adverse drug reactions in 18,820 patients in the United Kingdom, NSAIDs were responsible for 1.9 % (363) of all hospital admissions (29.6 % of all drug-related adverse events) in the period of time studied (67). The most frequent were gastrointestinal, nervous system, renal, and allergic adverse effects. Gastrointestinal toxicity is widely recognised, especially in the gastroduodenal area.

Over the past decade, an increasing quantity of data has been gathered documenting small bowel involvement and its importance, showing its previous underestimation. This is related to advancements in small bowel evaluation, especially in small bowel endoscopy. The goal of this review is to discuss current knowledge of the range of NSAID-induced small intestinal injury, its clinical features, diagnosis and management.

History

The first description of NSAID (aspirin)-induced gastropathy identified by endoscope was presented by Douthwaite and Lintott in 1938 (22). Small bowel damage due to indomethacin management was observed for the first time in humans in the 70s (80). Many cases of small bowel perforation (65) and other clinical manifestations of small bowel enteropathy were published (7, 8, 9, 10, 11, 12, 56) in the 80s. Most morphology data were acquired from autopsy (4) and surgical studies at that time (57). Because of the relative inaccessibility of the small intestine, initial endoscopy data were drawn from sonde enteroscopy, and were not published until the early 90s (64). The capsule endoscopy era begins in the year 2000 (44) and is linked with an information boom concerning NSAID-induced enteropathy.

Epidemiology

According to the data published in the ARAMIS (Arthritis, Rheumatism, and Aging Medical Information System) database, up to 1.3 % of patients treated with NSAIDs are hospitalised for severe gastrointestinal complications in the USA and Canada, a 1-year mortality rate is seen in about 0.11–0.22 % in this population (75).

NSAID-induced enteropathy is defined as acute or chronic small bowel dysfunction or structural damage related to NSAIDs. Epidemiology data are acquired from different sources, thus the presented prevalence is different according to the specific diagnostic method applied and target population. Small bowel ulcers were observed in 8 % of NSAID-treated patients in comparison to 0.6 % of controls (with no history of NSAID use) in a prospective, autopsy-based study (713 cases) (4). The endoscopically evident changes (including ulcers) were diagnosed by means of sonde or push enteroscopy in 41–66 % (62, 63, 64) and by means of capsule and double balloon enteroscopy in 16–88 % of NSAID users (30, 32, 36, 59, 60, 81). Other tests of small bowel damage and malfunction (faecal occult blood test, assessment of intestinal inflammation and permeability) confirm NSAID-enteropathy in 19–72 % (7, 8, 9, 10, 11, 12, 56, 83).

Pathogenesis

The pathogenesis of NSAID-enteropathy is more multifactorial and complex than formerly assumed but has still not been fully uncovered. The small bowel mucosa is exposed to the effects of NSAID several times in total. Initially, the local effect of the drug before and during its absorption, then the systemic effect, and finally the repetitive local effect after its enterohepatic circulation in some drugs plays an important role in the pathogenesis (20, 69). The use of enteric-coated, sustained-release, or slow-release NSAIDs may have shifted the damage to the distal parts of the gastrointestinal tract (small intestine and colon).

NSAIDs have a direct toxic effect on enterocytes (the result of high local drug concentration after peroral admission) well-described by the so-called “three hit hypothesis” (25). The first hit is represented by building of NSAIDs into the biological membranes and affecting their functions (the majority of NSAIDs are liposoluble weak acids). The increment in intracellular drug concentration leads to disruption of mitochondrial energy metabolism (uncoupling of oxidative phosphorylation) and adenosine triphosphate depletion (79). The second step is leakage of intracellular calcium and production of free oxygen radicals leading to the disruption of intra and intercellular integrity (tight junctions). The last hit is the consequence of increased intestinal permeability. Intraluminal content (such as bile acids, luminal bacteria and their degradation products, food macromolecules and other toxins) overcomes the weakened intestinal mucosal barrier and leads to inflammation (69). In experimental studies, NSAIDs did not induce enteropathy in germ-free rats or rats after bile duct ligation (46, 70). Nitric oxide formed by inducible isoform of nitric oxide synthase is often mentioned as another important factor in pathogenesis of NSAID-induced enteropathy. Experimental findings indicated that induction of a calcium-independent nitric oxide synthase involves intraluminal bacteria spectrum and leads to small bowel microvascular injury in the NSAID-treated rats (89). The NSAID-induced inhibi-

tion of local hydrogen sulphide production can also be associated with small bowel injury (24).

The second important pathogenetic mechanism in NSAID-induced enteropathy is the systemic effect represented by the prostaglandin depletion (cyclooxygenase – COX inhibition). The pathogenesis of enteropathy was initially thought to be associated with COX-1 inhibition only. However, it has been proven that selective COX-1 inhibition (or absence) does not lead to a gastrointestinal lesion, and selective COX-2 inhibition (or absence) leads to ileocaecal mucosa damage, different from “classical” NSAID-enteropathy (43, 76). Small bowel injury is induced by a combination of COX-1 inhibition with restricted mucosal blood flow and COX-2 inhibition probably through an unknown immunological effect (90).

All systemic and local pathogenetic mechanisms lead, according to inflammation intensity, to erythema, erosions and ulcers. The extensive fibroproduction during healing can cause strictures.

Clinical manifestation

NSAID-induced enteropathy usually remains clinically asymptomatic, its endoscopic diagnostics were not feasible previously and therefore NSAID-induced enteropathy was underestimated for a long time. Clinically evident serious events (bleeding, ileus and perforation) are infrequent, but potentially life-threatening (65).

a) occult gastrointestinal bleeding

The symptoms of NSAID-induced enteropathy are non-specific, the most frequent sign is obscure occult gastrointestinal bleeding. Bleeding correlates quantitatively with intestinal inflammatory activity and its intensity ranges from 2 to 10 ml per day.

b) overt gastrointestinal bleeding

Acute and overt gastrointestinal bleeding is a relatively rare symptom. The sources of bleeding are ulcers and erosions. NSAID-induced enteropathy is related to the 5–10 % of patients evaluated for obscure overt gastrointestinal bleeding (82).

c) NSAID-induced protein losing enteropathy

Another possible clinical manifestation of NSAID-induced enteropathy is protein-losing enteropathy (7). The amount of protein loss through inflamed small bowel mucosa is usually mild to medium and can remain up to 16 months after NSAID discontinuation (20).

d) jejunal and ileal dysfunction

Jejunal dysfunction can cause diarrhoea or can resemble celiac disease with malabsorption. The malabsorption is mostly milder and only rarely associated with malnutrition. Vitamin B12 and bile acid malabsorption can manifest itself through ileal dysfunction (14, 25).

e) small intestinal perforation and obstruction

Vasculitis was incorrectly considered the cause of small bowel perforation in some patients with rheumatoid arthritis treated with NSAIDs in the past. The case reports especially described small bowel perforations in patients treated with indomethacin. The typical symptoms can be disguised by the analgetic and anti-inflammatory effect of NSAIDs.

There is no significant correlation between the type of small bowel lesions and particular clinical manifestation (73) except diaphragmatic disease (5, 6, 40, 91). Diaphragm-like small intestinal strictures are a rare but very typical (pathognomonic) sign of NSAID-induced injury to the small bowel. These circumferential, purely fibrous, stenosing lesions are multiple (up to several tens), thin (1 to 4 mm thickness) and might cause severe small intestinal obstruction.

Diagnosis

In most patients, increased intestinal permeability and mucosal inflammation can be found in non-invasive laboratory tests. Those tests allowed the first objective confirmation of NSAID-induced enteropathy in the past. Above all, these days, diagnostics of NSAID-enteropathy is based on endoscopy. This fact is associated with enteroscopy development in recent years and is resulting in a rapid increase in sharing of information covering clinical procedure.

a) standard laboratory tests

Standard laboratory tests allow quick and easy identification of suspected small bowel injury in NSAIDs users, but are unusable for exact diagnostics because of their low specificity. Other possible causes associated with these findings should be excluded in differential diagnosis first. Positive faecal occult blood tests and sideropenic anaemia, as well as hypoalbuminaemia can be present. Sideropenic anaemia is observed in about 1–5 % of patients treated with NSAIDs. The aetiology of anaemia might be complex (35), resulting from chronic gastrointestinal bleeding, reduced iron and vitamin B12 absorption, malnutrition or features anaemia of chronic disease (in patients with rheumatoid arthritis) (77). A low serum albumin level was found in about 5–10 % of patients with rheumatoid arthritis (7).

b) small bowel permeability evaluation

Increased intestinal permeability in NSAIDs users with rheumatoid arthritis and osteoarthritis was discovered accidentally by Bjarnason in 1984 (12). Studies in healthy volunteers confirmed a rapid increase in intestinal permeability already within 12–24 h after NSAID ingestion (10). Although the spectrum of tests used in determination of small bowel permeability is relatively wide, its availability in clinical practice is low. The three most commonly used orally-ingested probes are saccharides (lactulose, mannitol), ethylene glycol polymers (polyethylene glycol) and non-degradable radionuclides ($^{51}\text{Cr-EDTA}$) with consequential detection of its urinary excretion. Detected prevalence rates depend on the sensitivi-

ty of the selected method and vary from 60 to 80 % (10, 12, 76, 78). The main limitation of these methods is their non-specificity and wide spectrum of different diseases, malnutrition, drugs and diets influencing intestinal permeability.

c) evaluation of intestinal inflammation

Intestinal inflammation is detectable after several days (61) on NSAID therapy in 44–70 % of patients and persists up to 16 months after discontinuation of treatment. It can be assessed by increased faecal excretion of ^{111}In and scintigraphic detection of its accumulation in the small bowel after intravenous administration of ^{111}In labelled leucocytes (8, 12, 76). The other possibility for small bowel inflammation testing is assessment of calprotectin (non-degradable protein produced mainly by neutrophils, monocytes and macrophages) in faeces indicating migration of these cells into the intestine (83).

The main disadvantage of both methods is low specificity for NSAID-enteropathy and the need for further investigation to exclude other possible causes of small bowel inflammation before a final diagnosis of NSAID-induced enteropathy could be set.

d) enteroscopy

The major advantage of enteroscopic methods is direct visualisation of small intestinal mucosa and identification of even tiny lesions along with the possibility of biopsy sampling in standard enteroscopies.

A wide spectrum of small bowel lesions is observed in patients treated with NSAIDs.

According to the severity of involvement, oedematous mucosa, focal and/or diffuse erythema (Fig. 1 a,b), red spots (Fig. 2), denuded area with loss of villous architecture, numerous lymphangiectasias (Fig. 3), petechiae, mucosal breaks (erosions - Fig. 4, aphthous lesions - Fig. 5 or ulcers - Fig. 6a,b), strictures and intraluminal blood (Fig. 7) are found. A few case reports of villous atrophy mimicking coeliac sprue (in patients treated with mefenamic acid or sulindac) have been reported (26, 45). No clear correlation between duration of NSAIDs' ingestion, NSAIDs' dose and enteropathy severity has been proven in studies published so far (59). Lesion localisation is influenced by the chemical and pharmacological attributes of the drugs administered - NSAIDs with enterohepatic circulation and slow release causing more distal lesions in the ileum and caecum. Small-intestinal diaphragms (Fig. 8) are rarely presented, but are the only one typical NSAID-induced lesion, which can be presented clinically as a small intestinal obstruction. This was first identified as a consequence of NSAIDs management by Lang et al. in 1988 (56). The diaphragms are multiple thin rings, comprised by mucosa and submucosa with profound fibrosis (with active inflammatory infiltrates at the top). The most typical localisation of these lesions is the ileum, jejunum and caecum. Prolonged treatment and use of high doses of NSAIDs are the main risk factors for diaphragm disease (1, 56, 72, 94).

Wireless capsule endoscopy

Wireless capsule endoscopy has become the leading imaging method in non-invasive diagnostics of small bowel involvement in NSAIDs-users (28). Capsule endoscopy studies confirmed small bowel lesions in 26–88 % patients treated with non-selective NSAIDs, 6–50 % patients treated with COX-2 selective NSAIDs, and 80 % of patients treated with low-dose aspirin (23, 29, 30, 32, 36, 59, 81).

The relative safety of COX2 selective NSAIDs in comparison to the non-selective ones indicated in short-term capsule endoscopy studies remains still controversial. The small bowel lesions compared in those studies are often thin and small mucosal breaks with problematical clinical significance. At another site, no difference was found in major lower gastrointestinal adverse events in a large randomised study comparing etoricoxib (60 or 90 mg daily) or diclofenac (150 mg daily) for an average of 18 months (54). One of the most surprising items of information from capsule endoscopy studies is the presence of small bowel lesions in about 7–41 % of healthy subjects or the controls, mostly small erosions and red spots. This fact somewhat complicated interpretation of results of the studies, because of the likely clinical insignificance of part of these findings identified by capsule endoscopy in NSAIDs users. Another possible limitation is the frequently insufficient differential diagnostics before or after capsule endoscopy to exclude other possible parallel causes of the described lesions (Crohn's disease, vasculitis, ischaemic enteritis etc.).

The last but not least of the problems represents lack of use of standardised terminology in some studies when describing small intestinal lesions.

Standard enteroscopy methods

Sonde and push enteroscopy used to diagnose NSAID-enteropathy in the 1990s were replaced by double (39, 93) or single balloon enteroscopies in the past decade. Inclusion of these methods in the endoscopy armamentarium introduced a revival of small bowel investigation and allowed an exponential accrual of our knowledge about small intestine diseases. Single balloon enteroscopy or spiral enteroscopy were introduced as alternatives to double balloon enteroscopy over the past few years (3, 84), but their value in NSAID-induced enteropathy diagnostics is still to be determined.

The importance of double balloon enteroscopy lies in differential diagnostics of lesions identified by means of capsule endoscopy with possible biopsy sampling and in the therapeutic potential of this method in case of complications (stenosis dilation, extraction of retained capsule endoscopy, control of bleeding) (50, 68). Histology investigation demonstrates only non-specific findings in small bowel mucosa in patients with NSAID-induced enteropathy. Histology confirmation is therefore not routinely needed (15). Double balloon enteroscopy is often indicated for ob-

scure gastrointestinal bleeding in patients treated with NSAIDs, small bowel lesions are detected in up to 51 % of these patients compared with only 5 % in controls (60). As regards other enteroscopy methods, push enteroscopy (due to its limited yield) and intra-operative enteroscopy (due to its invasive character) are used only rarely (2, 51).

Differential diagnosis

Correct diagnosis of NSAID-induced enteropathy can usually be made in conjunction with a good history and exclusion of other small intestinal diseases. The diaphragm is the only one pathognomonic lesion of NSAID-induced enteropathy. The other enteroscopy findings are more or less non-specific and thus differential diagnostics in NSAIDs users is a key problem before an efficient management choice is made. Crohn's disease must above all be excluded. Enteroscopy findings of segmental localised longitudinal ulcers and inflammatory polyps (cobblestone pattern), ulcerated or fibrous strictures and non-specific mucosal inflammatory signs define typical Crohn's enteritis. Although diagnostic when present, non-caseating granulomas are rarely detected in small bowel biopsy samples, so the histology is not the leading diagnostic method in patients with small bowel Crohn's disease. The other disorders we must take into consideration are infection diseases, especially in immunosuppressed and/or malnourished patients (tuberculosis, Yersinia, Cytomegalovirus and others), tumours (especially lymphoma endoscopically mimicking inflammation), Behcet's disease, ischaemic and radiation enteritis. NSAIDs are not the only ones drugs to cause small bowel lesions, the others (potassium chloride, warfarin, bisfosfonates and cytostatics) must be excluded, too. An interesting problem could be represented by differential diagnostics between NSAID-enteropathy and vasculitis present in patients with connective tissue or collagenous diseases in which both situations are possible. Small bowel involvement is present in some vasculitis (Churg-Strauss syndrome, periarteritis nodosa and Henoch-Schönlein purpura) more frequently.

Management and prevention

In spite of relatively intense research, there is still no effective, safe and tolerable drug treatment available in the market for management of NSAID-enteropathy. The main and most important management for patients with NSAID-enteropathy is still withdrawal of NSAIDs (41). Results of capsule endoscopy studies testify to some reduction of toxicity using COX-2 selective inhibitors, however the increasing information about adverse cardiovascular effects limits their usage (29, 30). Moreover the reduced prevalence of small bowel lesions in selective COX-2 inhibitors compared to non-selective NSAID users has not been confirmed over a longer time period (more than 3 months) (59).

The most evidence-supported management of NSAID-induced enteropathy is antibiotic treatment. Bacterial over-

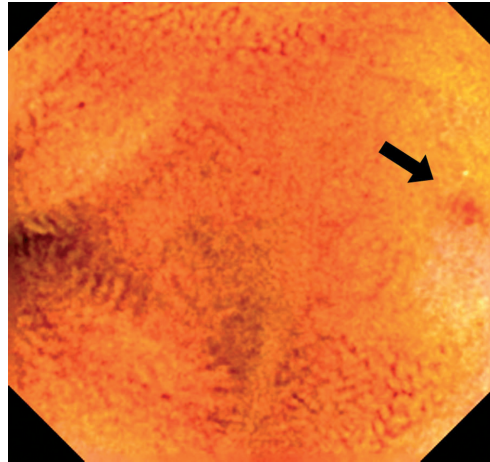
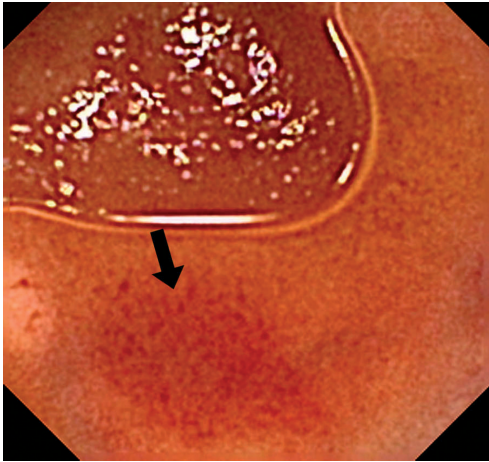


Fig. 1a,b: Non specific inflammatory changes of the jejunal mucosa - focal mucosal erythema (arrows) in a patient with long term NSAID therapy. Capsule endoscopy.

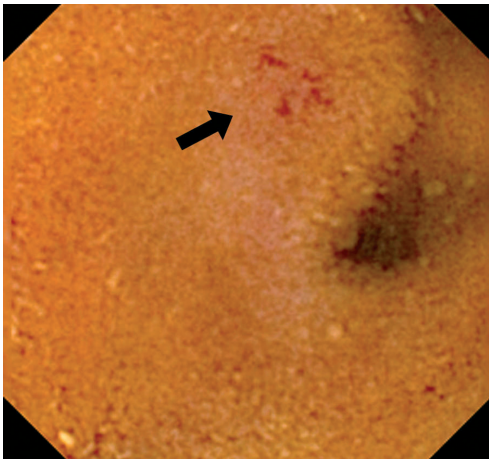


Fig. 2: Several red spots (arrow) in the jejunum of a patient with rheumatoid arthritis and long term NSAID therapy. Capsule endoscopy.

Fig. 3: Multiple whitish jejunal lymphangiectasias in a patient treated with NSAID. Capsule endoscopy.

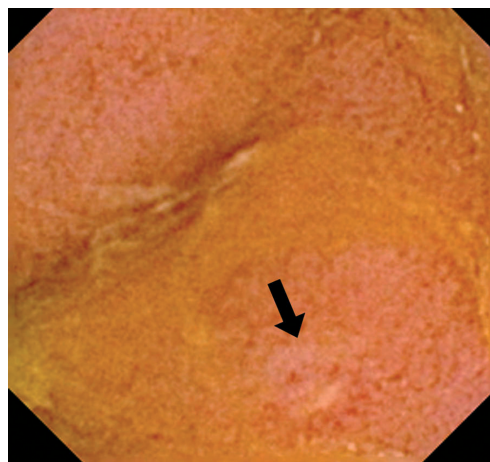
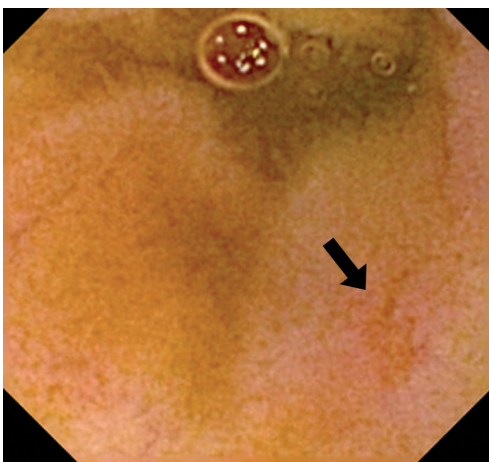


Fig. 4: Small linear erosions (arrow) in the proximal ileum in a patient treated with NSAID. Capsule endoscopy.

Fig. 5: Jejunal aphtha (arrow) in a patient with NSAID therapy. Capsule endoscopy.

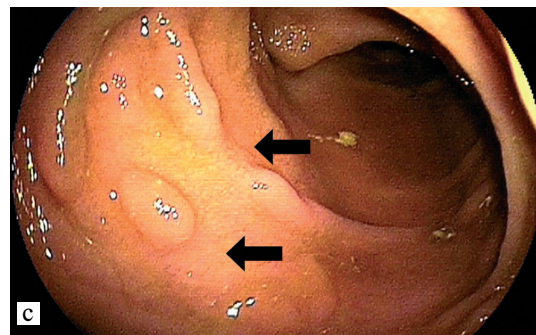
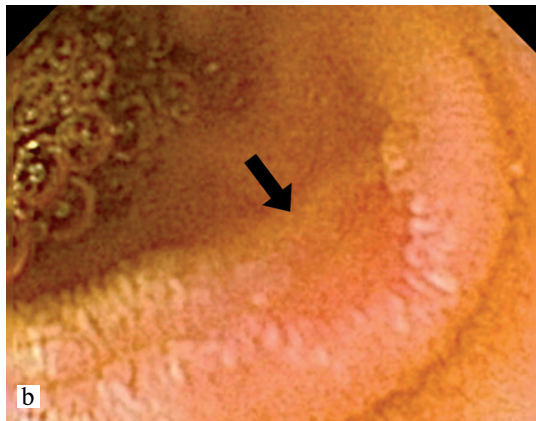
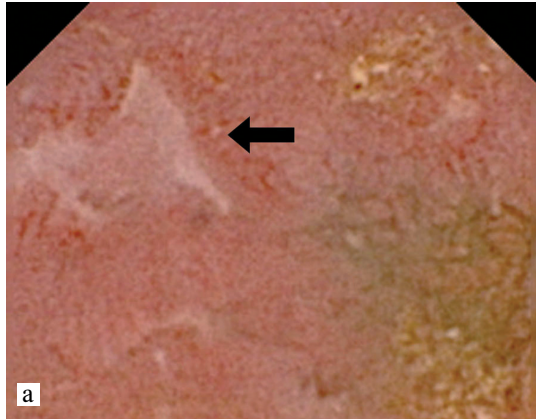


Fig. 6a,b,c: Small roundish (a) and linear (b) jejunal ulcers in a NSAID user (arrows, capsule endoscopy). c: Scars (arrows) in the area of healed ulcers of the proximal jejunum (double balloon enteroscopy).

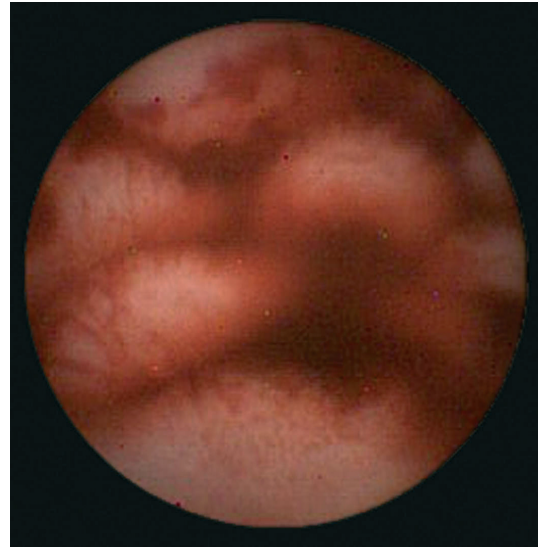


Fig. 7: Fresh blood in the distal jejunum in a chronic NSAID user. Capsule endoscopy.

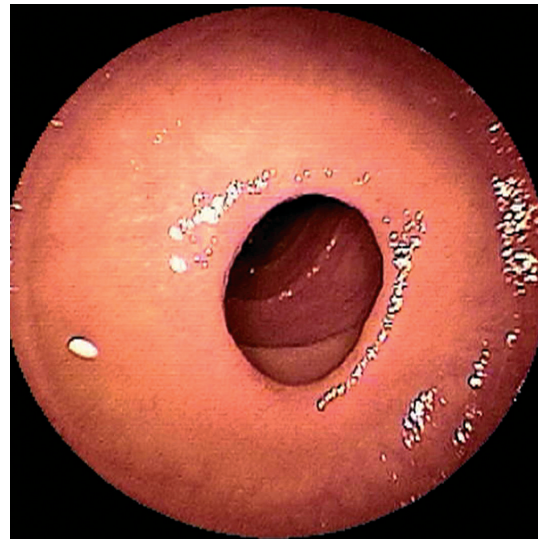


Fig. 8: Small bowel diaphragm - stricture caused by fibrous rings, submucosal fibromuscular hyperplasia covered with normal epithelium on histology. Double balloon enteroscopy.

growth in the ileum was identified in experimental animals on chronic NSAIDs therapy. The concurrent administration of purified Escherichia coli liposaccharide and NSAIDs facilitated ulcers in small intestine (34). Healing of small bowel indomethacin-induced lesions was observed after gram-negative bacteria eradication. Neutralisation of cytokines (TNF alpha, MCP-1) has a positive effect, too (88). It is clearly proven that antibiotic therapy (tetracycline, kanamycin, metronidazole, neomycin plus bacitracin) reduced NSAID-induced enteropathy (13, 17, 18, 53, 55). The positive effect of metronidazole on small intestinal NSAID-induced lesion healing and reduction of increased intestinal permeability in experimental rats has been repeatedly presented (58). The anti-oxidising effect aside from the antimicrobial one has also been considered (16, 17, 18, 92).

Owing to the key role of small bowel flora in NSAID-induced enteropathy pathogenesis, the use of probiotics/prebiotics altering intestinal microbiology and modulating the immune function seems to be reasonable. Despite this, study results are inconclusive. While some prebiotics were effective (21, 42), the tested probiotics failed to reduce the NSAID-induced increase of intestinal permeability in humans (31) and some increased the risk of small bowel injury in rats (48).

Sulphasalazine has been confirmed as producing antibacterial activity (71), with a preventative effect against an increase in intestinal permeability and anti-inflammatory activity in many previous studies (37).

Other disease-modifying antirheumatic drugs (like penicillamine, cloroquine and gold salts) were ineffective in the treatment of NSAID-enteropathy (38).

The efficacy of prostaglandin analogues (misoprostol) in preventing upper-GI injury from NSAIDs has been proven. Results from some studies also indicate its possible positive role in prevention and therapy in NSAID-induced injury to the small bowel (27, 87).

Potential anti-inflammatory and anti-oxidative effects of protein pump inhibitors (lansoprazole, presented in some works with experimental animals) (52), have not been confirmed in human capsule endoscopy studies (29, 30).

Although the NO-donating NSAIDs have produced significantly less gastrointestinal injury, than original NSAIDs from which they are derived, in published studies (19, 85, 86), they are not affordable for the clinical practice yet. Hagiwara et al. investigated the preventive effect of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors on NSAID-induced ulcers in the small intestine of rats. Fluvastatin, which was reported to have antioxidative activity (but not the other HMG-CoA reductase inhibitors pravastatin and atorvastatin), provided a protective effect against the formation of NSAID-induced ileal ulcers in rats (33). Other drugs like repamide and tacrolimus were also tried in healthy volunteers and in experimental studies on NSAID-enteropathy with promising results (49, 66).

Endoscopic and/or surgical treatment can be indicated in case of complications (strictures, bleeding, perforation) (47).

Conclusions

In conclusion, NSAID therapy causes small bowel lesions in a significant section of patients. Although the clinical importance of NSAID-enteropathy is often limited, it can lead to severe complications. The most frequent signs are anaemia and/or hypalbuminaemia. Enteroscopy (capsule endoscopy or double balloon enteroscopy) has become the most sensitive and most frequently used diagnostic method in identifying of mucosal breaks, small intestinal diaphragms or other types of small bowel lesions. Despite the progress in diagnostics and increased information on pathogenesis and epidemiology, the prevention and management of NSAID-induced enteropathy still remains controversial. Double balloon endoscopy has an important role in the management of complications of NSAID-enteropathy (especially bleeding and strictures).

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