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## EDITORIAL

# Non-steroidal Anti-inflammatory Drug-Induced Enterocolopathy: The Continuing Search for Treatment and Prevention

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## ABSTRACT

Long-term as well as short-term treatment with non-steroidal anti-inflammatory drugs (NSAID) leads to the development of gastrointestinal tract (GIT) complications during the course of treatment. Complications, such as bleeding, perforation, and obstruction, commonly affect the upper GIT. However, the lower GIT may also be severely affected with NSAID-induced enterocolopathy which occurs more frequently in the small bowel and to a lesser extent in the large bowel. Enterocolopathy is more difficult to treat than NSAID-induced upper GI injury, and to date, there is no proven effective therapy. As the current treatment focuses mainly on the withdrawal of the causative drug, the management is now shifting towards prevention. The search for effective prevention is continuing,

and new prevention strategies such as the use of probiotics, teprenone, and others are emerging. They are showing promising cytoprotective properties in the healing of NSAID-induced ulcers. Unfortunately, most of the available evidence on the prevention and treatment is based on animal studies and sporadic case reports in the absence of large randomized controlled studies. This calls for a consolidated effort to establish evidence-based guidelines on the prevention and treatment of NSAID-induced enterocolopathy to halt its rising incidence.

**Key words:** Non-steroidal anti-inflammatory drugs; Complications; Enteropathy; colopathy; Proton-pump inhibitors; Probiotics; Teprenone; Prevention

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## INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for many patients with chronic ailments such as rheumatoid disease and musculoskeletal disorders due to their anti-inflammatory, anti-pyretic, and analgesic properties<sup>[1,2]</sup>. However, their use is associated with the development of gastrointestinal (GI) mucosal injury, ranging from inflammation, erosions to ulcers and their subsequent complications. It is estimated that 1-2% of NSAID users experience serious GI complications such as bleeding, perforation, and obstruction during the course of the treatment<sup>[3]</sup>. Although GI complications are more common in chronic users, short-term users of NSAIDs are by no means immune to serious complications<sup>[4]</sup>. These complications commonly affect the upper GIT, but the lower GIT may also be severely affected with what is called NSAID-induced enterocolopathy. The enterocolopathy occurs more frequently in the small bowel and to a lesser extent in the large bowel in more than 60% of long-term users, and the evidence of

macroscopic mucosal injury to the small intestine is usually apparent after 2 weeks of slow-release NSAID ingestion, in more than 65% of healthy volunteers<sup>[5]</sup>.

In recent years, NSAID-induced entero-colopathy is attracting the researchers' attention, and 3 issues warrant future research. First, whether the mucosal injury is the result of a local 'direct' or systemic effect; second, the timing of the injury in relation to the duration of ingestion (chronic use vs. short-term use); and third, if the oral route is associated with greater injury than the parenteral one (oral vs. parenteral).

#### Local vs. Systemic effect

The NSAID damage starts as mucosal inflammation which progresses over the course of several months to superficial and deep ulcerations of variable sizes. The right colon seems to be most commonly affected in colopathy; probably due to the increasing use of enteric-coated and slow-release medications allowing more of the drug substance to reach the right colon and exerting its detrimental direct 'local' effect<sup>[6]</sup>. However, the left colon and rectum can be the sole site of colopathy after NSAID ingestion<sup>[7]</sup>. This may argue against the direct/'local' effect theory of NSAIDs and supports the systemic effect hypothesis. It seems more likely that the damage to the intestinal mucosa is due to the combined pre-absorption local and post-absorption systemic effects. Nevertheless, this needs to be settled by future research and studies.

#### Timing of the injury and treatment duration

It is generally believed that mucosal damage usually occurs years during the course of treatment. However, long-term drug use is not a requirement for its development, and short-term therapy can be just as significant in causing colitis even after a few days of NSAID use, and the mucosal ulceration may occur as early as 2 months after NSAIDs ingestion<sup>[8,9]</sup>. This means that the injury can occur any time, but more likely after chronic use. Moreover, the mucosal injury may occur regardless of the dose; even low doses of NSAIDs, as low as 2 tablets of diclofenac, can result in GI complications ranging from ulcers and severe life-threatening bleeding<sup>[7,10]</sup>.

#### Oral vs. Parenteral NSAIDs

Entero-colopathy can occur after either the oral or parenteral forms of NSAIDs. The suppository forms of NSAIDs can also cause rectal damage in the form of inflammation (proctitis), ulcerations, and strictures formation<sup>[11]</sup>. This means entero-colopathy may develop after oral ingestion, parenteral administration, or transanal topical applications of NSAIDs. However, which route is associated with more mucosal damage and complications is yet to be substantiated.

## PATHOGENESIS

NSAID entero-colopathy is more complicated than NSAID gastropathy. The exact pathogenesis remains entirely undefined, and its cause is multifactorial. The '3-hit hypothesis' suggests that NSAIDs directly damage the phospholipid in the cell membrane of the intestinal mucosa which subsequently damages the cell mitochondria. This, in turn, causes a decrease in energy synthesis, resulting in calcium efflux, free radicals generation, and an increase in mucosal permeability. Finally, as a result of the increased permeability, intraluminal contents such as digestive enzymes, bacteria, bile acids, and toxins translocate causing inflammatory injury<sup>[12]</sup>. The GI lesions caused by NSAIDs' long-term administration are, therefore, characterized by a breakdown in epithelial tight junctions, reduction in mucus production, the abnormal passage of luminal antigens

and intestinal bacteria, and an increase in the local and systemic inflammatory responses<sup>[13]</sup>.

Several other pathophysiological mechanisms have been postulated. They include decreased prostaglandin synthesis, cyclooxygenase (COX) inhibition, Gram-negative bacteria overgrowth, the combination of bile acid action in addition to NSAIDs action, and imbalance in the gut microflora (dysbiosis). Prostaglandins are derived from COX-1 and are important for maintaining intestinal mucosa homeostasis. Hence, COX-1 inhibition leads to prostaglandin depletion with a subsequent increase in intestinal permeability and GI mucosal damage. In contrast, COX-2 inhibition is not usually associated with GIT damage<sup>[14]</sup>. However, another animal model study indicated that COX-2-derived prostaglandins also play a role in the maintenance of intestinal integrity, repairing the mucosal injury, and halting inflammation<sup>[15]</sup>. Gram-negative bacteria invade the mucosal membrane activating specific lipopolysaccharide 'toll-like' receptors, which stimulates the inflammatory response with subsequent intestine mucosal damage<sup>[16]</sup>. It is also postulated that the enterohepatic circulation of NSAIDs plays a role, by causing repeated and continuous exposure of the intestines to the drug, enhancing the intestinal damage<sup>[17]</sup>.

Growing evidence suggests that gut microbiota, which is composed of a diverse community of microorganisms including bacteria, viruses, fungi, and parasites, plays a critical role in the progress of entero-colopathy. In a healthy state, it promotes food digestion and participates in the gut immune function<sup>[18]</sup>. Any change in the composition of gut microbiota from any reason may promote the development of diseases such as colorectal cancer, inflammatory bowel disease, and possibly entero-colopathy<sup>[19]</sup>. It seems that the chronic use of NSAIDs changes the composition of the intestinal bacteria and aggravates bile acids cytotoxicity. Moreover, NSAIDs also impair the intestinal barrier by cyclooxygenase inhibition and mitochondria destruction, leading to intestinal bacteria translocation, and the production of nitric oxide and pro-inflammatory cytokines predisposing to intestinal injury<sup>[20]</sup>.

## SIGNS AND SYMPTOMS

In most cases of NSAID-induced entero-colopathy, the damage is subclinical in the form of inflammation, erosions, or ulceration. The presentation often varies from abdominal pain, altered bowel habits, weight loss, iron-deficiency anemia, to bloody diarrhea, protein-losing enteropathy, and GI bleeding<sup>[21]</sup>. Patients with small bowel ulcers may present with bleeding or perforation with peritonitis. Some patients with pre-existing diverticulosis may present with diverticular bleeding or perforation with subsequent peritonitis. Some NSAIDs may also exacerbate a pre-existing inflammatory bowel disease. Chronic users may also present with the manifestations of diaphragm disease. The presence of bowel diaphragms may remain asymptomatic or it may cause intestinal obstructive symptoms which necessitate surgical or endoscopic intervention.

## DIAGNOSIS

The Diagnosis is made by the history of short- or long-term NSAIDs therapy, and the endoscopic findings of a non-specific entero-colitis that resolves partially or completely within six weeks of the offending NSAID withdrawal. The introduction of different enteroscopy modalities such as wireless capsule endoscopy and double-balloon enteroscopy has allowed the visualization of NSAID-induced small bowel lesions. The injuries may be recognized by their endoscopic characteristic features such as the presence of multiple, superficial to

deep ulcers with an irregular arrangement and < 1 cm in diameter<sup>[22]</sup>. Also, the histological features on biopsy obtained through endoscopic modalities show non-specific inflammation and exclude other differentials such as Crohn's disease, ulcerative colitis, and tuberculosis<sup>[22]</sup>. The computed tomography and magnetic resonance imaging scans are especially helpful in diagnosing NSAID-induced small and large bowel diaphragms and strictures where the use of wireless-capsule enteroscopy is contraindicated<sup>[23]</sup>.

NSAID-induced entero-colopathy may be misinterpreted endoscopically and histologically as Crohn's disease<sup>[24]</sup>. Other differential diagnoses include intestinal tuberculosis, and in the case of colopathy, it could be mistaken for ulcerative colitis, ischaemic colitis, pseudomembranous colitis, and radiation colitis.

## THE INCREASING INCIDENCE OF ENTERO-COLOPATHY

In recent years, hospitalization due to NSAID-induced upper GI complications has declined as a result of the concomitant administration of gastro-protective drugs. On the contrary, there is a significant increase in lower GI tract complications as a result of NSAID entero-colopathy<sup>[3]</sup>. This is attributed to the increasing use of slow-release and enteric-coated preparations of NSAIDs making more drug substances reach the right-side of the colon inflicting some detrimental effects. Also, recent studies suggest that proton pump inhibitors (PPIs) and other commonly used drugs for protecting the gastro-duodenum do not offer the same beneficial protective effect to the lower GI tract. Moreover, they may significantly worsen NSAID-induced damage in the small and large intestines by altering the intestinal microbiota and hence implicated in increasing the risk of lower GI injury especially bleeding<sup>[25]</sup>. Furthermore, long-term use of PPIs causes small bowel malabsorption of certain nutrients and vitamins, resulting in osteopenia with subsequent bone fractures<sup>[26]</sup>. This calls for future research to be directed toward identifying patients at low risk for NSAID-induced upper GI ulcers to avoid the concomitant administration of PPIs with its subsequent damage to the lower GIT<sup>[27]</sup>. Furthermore, the increasing incidence of NSAID-induced entero-colopathy calls for a consolidated effort to find a preventative strategy or treatment therapy.

## TREATMENT AND THE CONTINUING SEARCH FOR PREVENTION

The treatment is more difficult than that of NSAID-induced upper GI injury<sup>[21]</sup>. Unfortunately, until now, there is no available therapy that can treat NSAID entero-colopathy. The treatment is focused mainly on the withdrawal of the causative drug. However, this is not always a clinically feasible option in patients who are entirely dependent on NSAIDs for pain relief<sup>[28,29]</sup>.

Several preventive strategies have been recommended. Gastric acid secretion is associated with the pathogenesis of NSAID-induced upper GI damage. Hence, the concurrent administration of acid-suppressing PPIs to prevent NSAID-induced GI side-effects is recommended<sup>[30]</sup>. However, as mentioned above, long-term administration of PPIs is associated with the increased risk of malabsorption, infections, and fractures<sup>[3]</sup>. Therefore, selective COX-2 inhibition has emerged as a potential alternative to NSAIDs in the reduction and prevention of damage in the lower GI tract by preventing prostaglandin deficiency<sup>[29]</sup>. Data suggests that celecoxib, meloxicam, and rofecoxib may have less small bowel toxicity than non-selective NSAIDs. However, the possible side effects on the

colon are not well-known. Rofecoxib has been implicated as a cause of acute hemorrhagic colitis after five days of therapy; it resolved after the drug was stopped<sup>[31]</sup>. Also, a major concern regarding highly selective COX-2 inhibitors is cardiovascular toxicity and this has limited their role in prevention.

The use of steroids has been advocated in some cases of NSAID-induced colonic strictures, but their routine use is cautioned in the absence of robust evidence of effectiveness<sup>[32]</sup>.

Since Gram-negative bacterial endotoxins contribute greatly to mucosal ulceration, antibiotics that target Gram-negative bacteria have been advocated, but the evidence is inconclusive. Also, metronidazole reduces intestinal inflammation and bleeding due to NSAIDs, but it does not affect intestinal permeability<sup>[33]</sup>. This proven effectiveness was shown in animals, but it has not been properly tested in humans<sup>[34]</sup>.

The protective effect of 5-aminosalicylic acid in NSAID entero-colopathy was demonstrated by the application of sulphasalazine or mesalazine for 4 weeks which showed a decrease in the small intestinal mucosal lesions caused by some NSAIDs<sup>[35]</sup>. In addition, anti-TNF therapy was found, in a clinical study, to decrease the risk of NSAID enteropathy in rheumatoid arthritis patients, and hence could play a potential role in the future treatment of NSAID-induced entero-colopathy<sup>[36]</sup>.

Prostaglandin suppression makes the intestinal mucosa susceptible to the damaging effect of intraluminal contents such as acid, bile, bacteria, digestive enzymes, and drugs such as NSAIDs<sup>[37]</sup>. Currently, the only available prostaglandin is misoprostol, a synthetic prostaglandin E1 analog. A series of randomized controlled trials (RCTs) in normal volunteers have shown that this agent can prevent acute NSAID-related erosion and ulceration<sup>[38-40]</sup>. RCTs in patients with OA and RA have also demonstrated that misoprostol was significantly better than placebo, sucralfate, and ranitidine for the prevention of NSAID-related gastric ulcers<sup>[41]</sup>. However, the benefit of prostaglandins in entero-colopathy is not well defined. Unfortunately, till now there is no evidence that prostaglandins or any other therapeutic agent prevent or reduce NSAID injury to the bowel.

As hydrogen sulfide is an important endogenous mediator in GI mucosal defense, it was used in rats to protect against NSAID enteropathy with good results. It acts by reducing the bile cytotoxicity and preventing dysbiosis<sup>[34]</sup>.

Diet manipulation may also protect against NSAID entero-colopathy, for example, monosodium glutamate (MSG), a substance is known to enhance the flavor of foods, and glutamine, a derivative of glutamic acid, have been reported to protect the stomach against NSAID-induced damage and enhance the healing of acute or chronic gastric ulcers in experimental animals. A similar protective effect was found in NSAID-induced enteropathy in rats<sup>[43]</sup>. Herbal remedies such as sulforaphane (a phytochemical found in abundance in broccoli sprouts) were also found to potentially induce a variety of antioxidant enzymes that protects against mucosal cell injury produced by chronic oxidative stresses induced by NSAIDs *in vivo*<sup>[44]</sup>.

## PROMISING NEW TRENDS IN PREVENTION

NSAID's long-term administration often causes gastrointestinal lesions characterized by increased local and systemic inflammatory responses<sup>[13]</sup>. In a murine model, probiotics dampened several local and systemic markers of an inflammatory process, as well as increasing the secretion of IL-10 by regulatory T-cells. Also, probiotics induced favorable changes in the large intestine microbiota characterized by an increase in anaerobes and lactobacilli, and a significant decrease in total enterobacteria. Hence, it seems that oral

probiotic supplementation increases intestinal antimicrobial activity and reinforces the intestinal epithelial barrier in NSAID-induced inflammation by maintaining intestinal homeostasis<sup>[45]</sup>.

Prebiotics are specialized plant fibers that act as nutrients to the bowel microbiota promoting and maintaining good intestinal homeostasis. There are only a few studies on prebiotics in NSAID entero-colopathy. However, it has been reported that prebiotic lactoferrin alone prevented NSAID-induced enteric damage<sup>[46]</sup>. Also, the soluble dietary fibers, especially pectin, guar gum, and polydextrose were found to protect against NSAID-induced damage in the small intestine of cats<sup>[47]</sup>. This highlights the beneficial effects of probiotics and prebiotics in experimental models of NSAID enteropathy<sup>[48]</sup>. However, their potential protection in NSAID-induced entero-colopathy in humans needs further clinical studies.

Another promising drug is a terpene analog called teprenone or geranylgeranylacetone. It has cytoprotective properties that aid in the healing of gastric ulcers and the treatment of gastritis. It is commonly used in several Asian countries as an anti-ulcer drug. It prevents mucosal injury caused by NSAIDs without affecting gastric acid secretion<sup>[49]</sup>. Animal studies have demonstrated that teprenone can prevent NSAID-induced gastric as well as small intestinal injuries<sup>[50,51]</sup>. However, its effect on colonic damage was not studied. Although this drug has also been tested in several human trials, there is no robust analysis to guide clinical practice. A recent systematic review and meta-analysis of 6 RCTs comparing teprenone with control indicated a statistically significant reduction in the risk of GI adverse events in patients receiving teprenone as compared to control after 12 weeks ( $p = 0.01$ ). This evidence -though was considered of low quality- indicates a beneficial role of teprenone in preventing GI injuries in patients receiving long-term NSAIDs<sup>[52]</sup>. As the drug is used in certain Asian countries, the results of this meta-analysis cannot be generalized on a global scale. Furthermore, the majority of the analyzed RCTs (5 out of 6) looked at the effect of teprenone on the upper intestinal injuries, and only one study looked at the effect of teprenone on small bowel injury. In this lone RCT, the severity of small bowel mucosal injury was significantly higher in the control group vs. the teprenone group<sup>[53]</sup>. This calls for high-quality RCTs comparing the effect of teprenone in patients with entero-colopathy versus treatment with placebo or other cytoprotective drugs. This certainly strengthens current evidence and establishes evidence-based guidelines on the treatment and prevention of NSAID-induced entero-colopathy.

There is a tireless effort to find a treatment or at least prevention for NSAID-induced entero-colopathy. Most if not all of the studies are addressing NSAID enteropathy and little attention is paid to colopathy. The paucity of studies on colopathy may be attributed to its lower incidence than enteropathy. Unfortunately, there is no sufficient data to support any type of prophylactic therapy directed at the prevention of NSAID-related injury to the colon. Moreover, the published studies are confined mainly to experimental animal models and have not yet been translated into clinical practice. This calls for the translation of promising animal studies to the clinical setting and conducting robust RCTs. The meta-analysis of those trials will certainly provide the medical community with a strong evidence-based guideline for the management of NSAID-induced entero-colopathy.

## CONCLUSION

The incidence of NSAID-induced injury to the lower GIT is on the increase with a good proportion of patients presenting with GI com-

plications. The mucosal damage may occur even after a short course of the medication. Once the diagnosis is made, treatment is by cessation of the causative drug. Recently, there is a consolidated effort to find an effective preventative therapy that is not associated with any adverse events to either the upper or lower GIT. Some new preventative strategies are emerging and are promising. Unfortunately, most of the available evidence on the prevention and treatment of NSAID entero-colopathy is based on animal studies and sporadic case reports in the absence of large randomized controlled studies. Well-conducted RCTs are urgently needed to establish evidence-based guidelines on the prevention and treatment of NSAID-induced entero-colopathy.

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