Underestimation of clinical importance of non-steroidal anti-inflammatory drug induced enteropathy and its exacerbation by proton pump inhibitors

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Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used over-the-counter to relieve pain and symptoms of arthritis and soft tissue inflammation. Proton pump inhibitors (PPIs) are often used simultaneously with NSAID to protect against its gastroduodenal side effects. However, the suppression of gastric acid secretion by PPIs does not seem to protect against the damage caused by NSAIDs in the more distal small intestine, often called as NSAID induced enteropathy. In fact, the small intestine seems to be more susceptible to the damaging effects of NSAIDs than the stomach[1] and PPI may even exacerbate the NSAID induced enteropathy.[2]

The main reason of the unawareness and the underestimation of NSAID enteropathy is the difficulty in making a diagnosis. Its diagnosis is often based on the following tests, as evidenced by the previous studies:

1. The use of ^{51}Cr-EDTA or the differential urinary excretion of ^{51}Cr-EDTA or lactulose/mannitol or rhamnose given with or without osmotic fillers detected the increased intestinal permeability caused by NSAID in 50%–70% of patients, but the test is non-specific.[3]
2. Four day fecal excretion of ^{111}Indium labeled white cells showed the presence of NSAID enteropathy in 50%–70% of patients, but the test is expensive.[3]
3. Fecal calprotectin (a non-degraded neutrophil cytosolic protein) showed the presence of NSAID enteropathy in 44% of patients receiving NSAID.[4] However, this test is again non-specific as the raised levels of fecal calprotectin are also seen in inflammatory bowel disease and colorectal cancer.[5]
4. Enterescopy showed NSAID enteropathy in 47% of patients with rheumatoid arthritis on NSAIDs.[6]
5. Wireless Capsule endoscopy (WCE) detected NSAID enteropathy in 68% of patients.[7]

Although WCE visualizes the entire small bowel, fecal reflux into the terminal ileum often prevents optimal visualization of this area, Because of the predilection of NSAID for damage in the distal ileum,[8] terminal ileoscopy should be performed at all colonoscopies. In fact, terminal ileoscopy might be complementary in the diagnosis of NSAID enteropathy.

Whereas inhibition of mucosal cyclooxygenase -1 and -2 leads to the gastroduodenal damage, the mechanism of NSAID on mid or distal small intestine is different. The NSAID induced enteropathy seems to be mediated by intestinal permeability, enterohepatic circulation and bile. The injury of small intestinal is contributed by neutrophil infiltration, release of tumor necrosis factor-alpha and the increase in gram-negative bacteria in the small intestine.[2] The clinical features of NSAID enteropathy may be unremarkable, but some complications can be subtle or potentially life threatening. It can lead to chronic iron deficiency anemia due to the continuous and mild bleeding from the small bowel ulcerations, the amount of blood loss in most cases being 2–10 ml/day.[9] The other complication can be protein losing enteropathy, which can result in hypoalbuminaemia.[9]

The injury of small intestine was demonstrated in healthy volunteers consuming NSAID and PPI for 14-16 days.[10] Microscopic colitis was found to be more common among both NSAID and PPI users.[11] Recent animal studies demonstrated that PPI may exacerbate NSAID enteropathy by changing the small intestinal bacteria.[2] In this study, omeprazole was given to the rats, and this was associated with a significant increase in the aerobic bacteria (both gram-negative and gram-positive) in the jejunum, but a significant reduction (80%) in *Actinobacteria* and *Bifidobacteria* spp.[2] The intestinal ulceration or bleeding in response to omeprazole or naproxen was prevented by administering *Bifidobacteria*.[2]

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Use of PPIs has also been associated with a significant increase in the incidence of various infections, most notably *Clostridium difficile*.[12] Absorption of calcium, iron, magnesium and vitamin B12 can be impaired, and increased rates of osteoporosis-associated bone fractures in patients chronically treated with PPIs were also found in the study.[13]

Therefore, a careful assessment of the use of PPIs together with NSAIDs is warranted. The benefits of the protection from gastroduodenal damage with PPI therapy could be offset by more distal damage, which is more difficult to detect.The suggested prevention and treatment strategies for NSAID induced enteropathy are given below:

1. The offending drugs should be withdrawn as far as possible.
2. Misoprostol, which has an established role in preventing NSAID induced gastroduodenal adverse effects, has also been found to decrease the incidence of more distal intestinal damage due to NSAID, as assessed by video capsule endoscopy.[14]
3. Novel NSAID with fewer gastrointestinal adverse effects are under development. Nitric Oxide-releasing NSAIDs were found to be better tolerated in the small intestine in animal studies[15] and in a clinical trial, to cause less increase in small intestinal permeability than the parent drug (naproxen).[16] Hydrogen sulphide-releasing NSAIDs have been shown to cause negligible damage in the small intestine of rats,[17] but have not yet been evaluated in humans.
4. Metronidazole with indomethacin resulted in a significant reduction in NSAID induced intestinal permeability in volunteers.[18] However, long term use of metronidazole is not justified in the clinical setting.
5. The NSAID enteropathy and inflammatory bowel disease have got the similar pathological findings which led to the suggestion that sulphasalazine may be a possible therapeutic drug in NSAID enteropathy.[19] In one study, Sulphasalazine significantly reduced the intestinal inflammation and blood loss in patients taking NSAIDs.
6. There may be a possible role of prebiotic and probiotic in NSAID enteropathy. Animal studies showed that a lactate-producing species of *Bifidobacteria* significantly reduced the severity of NSAID enteropathy in rats, while a species of *Bifidobacteria* not producing lactate had no effect.[20] Lactate-producing *Bifidobacteria* may be a viable prophylactic therapy for NSAID enteropathy. However, further study is required to establish the role of probiotic in alleviating the NSAID enteropathy in human being.

In conclusion, since NSAIDs and PPIs are widely used concomitantly and also available without prescription, additional studies are needed to explore their associations with enteropathy on humans, and if patients, receiving both classes of medications, present with diarrhea, abdominal distention, flatulence, or abdominal pain, they should be reassessed for the enteropathy and treated accordingly

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