



NSAIDs-induced Gastrointestinal Disorders

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ABSTRACT

Non-steroidal anti-inflammatory drugs are widely used drugs. These drugs have significant adverse effects. NSAIDs affect the entire GI tract, with predominant stomach and duodenal injury. Esophagitis, bleeding gastroduodenal ulceration, small bowel enteropathy, in the form of strictures or diaphragms, and colonic ulcerations are some examples of NSAID-induced gastrointestinal injuries. Upper or lower GI endoscopy or barium imaging are used as diagnostic tools. Major factors contributing to adverse effects on these organs are multifactorial with cyclo-oxygenase enzyme inhibition being the prime mechanism leading to lack of prostaglandins which are the fundamental in mucosal protection. Old age, prior complicated GI events, concomitant use of warfarin or steroids are some of the risk factors for development of NSAID related peptic ulcer. The clear guidelines regarding *H. pylori* and NSAIDs in causation of GI injury and its prevention is still unclear. Knowledge of COX 1, COX 2 components of cyclo-oxygenase enzyme and their respective role in inflammation cascade has led to the discovery of several selective NSAIDs and most recent NO donating NSAIDs. Use of PPI, Misoprostol, selective NSAIDs, combination of PPI and NSAIDs seem to be useful options for specific situations when NSAID intake is indicated.

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used over-the-counter (OTC) drugs worldwide. Though the extent of their usage in the Indian population is not known, it is likely to be large. Their major usage is as casual prescription for their analgesic and anti-inflammatory action, and in organized rheumatology and orthopedic practice. These drugs have also been found to have chemo-preventive potential in gastrointestinal (GI) cancers.

However, their use is associated with a wide range of adverse GI effects. The entire GI tract along with the liver and pancreas is prone to adverse events due to consumption of these drugs for short or long duration. Sufficient evidence is now available regarding the mechanisms of development of mucosal damage due to these drugs and also about contributing risk factors, and the role of the type, dose and duration of NSAID used in causing them. Drugs that can prevent as well as heal these injuries have also been recognized.

PATHOGENESIS OF NSAID-RELATED MUCOSAL DAMAGE

This is essentially multifactorial. Two broad patterns of injury have been identified: topical and systemic. These are cyclo-oxygenase independent and dependent, respectively.

NSAID ingestion leads to denudation of mucosal epithelial cells and increased anion exchange. This leads to decrease in transmucosal potential,¹ which allows the drug to enter the cell. With change in pH of the milieu, the NSAID accumulates

inside the cell and results in local damage. These mechanisms are either dependent or independent of the cyclo-oxygenase pathway and also involve attenuation of the phospholipid membrane and surface hydrophobicity of gastric mucosal layer.² The local effects are mainly erosions and acute hemorrhages.

Support for a systemic effect of NSAIDs on GI mucosa comes from certain observations.³ These include an increased or similar incidence of gastric ulcers with the use of enteric- or non enteric-coated NSAIDs, and also the occurrence of gastro-duodenal ulcers during the use of NSAIDs as rectal suppositories or by the parenteral route.

Cyclo-oxygenase dependent effects

Cyclo-oxygenase is an enzyme that exists in two forms, viz., COX 1 and COX 2. It acts upon arachidonic acid in cells containing phospholipids in their wall, resulting in the formation of various types of prostaglandins (PG E₂, F₂ and F₂ alpha in humans). Prostaglandins are crucial in maintaining mucosal integrity by various mechanisms, including maintenance of mucosal blood flow, stimulation of secretion of gastric mucus, maintaining mucosal bicarbonate content, and prevention of disruption of gastric mucosal barrier.

COX 1 is present in most human tissue, especially in GI mucosa and platelets. COX 1 inhibition leads to PG inhibition along with decrease in platelet aggregation. Inhibition of COX 2, which is inducible through actions of cytokines, endotoxins and growth factors, causes selective inhibition of PG. Non-specific NSAIDs,

which inhibit both COX 1 and COX 2, result in reduction of inflammation, pain, fever and similar effects of inflammation by causing PG inhibition but exposes gastric and duodenal mucosa (predominantly) to their toxic effects of uninhibited thromboxane effects. Older-generation NSAIDs (aspirin, ibuprofen, naproxen, ketorolac) are non-selective, whereas rofecoxib and celecoxib represent a group of selective or COX 2 inhibitors.

Other mechanisms of NSAID-related GI injury

The fact that there is poor correlation between gastric mucosal injury and degree of prostaglandin suppression implies other mechanisms of mucosal injury.^{4,5} NSAIDs augment pepsinogen secretion via a mechanism that is independent of PG and is possibly brought about via a calcium-dependent post-receptor mechanism.⁶ Active immunization against PG has shown to increase GI ulcers⁷ and exogenous supply of PG⁸ helps to prevent development of NSAID-related ulcers.

NSAIDs are known to directly inhibit gastric mucosal blood flow, reduce duodenal bicarbonate secretion and augment gastric acid secretion. It is possible that these effects are prostaglandin-mediated. Neutrophils also appear to contribute to NSAID-related mucosal damage. These cells adhere to the vascular endothelium of the stomach and mesenteric circulation via intercellular adhesion molecules (ICAMs). Induction of neutropenia or pretreatment with monoclonal antibodies against these adherence sites seems to prevent NSAID-related ulcers.

CLINICAL MANIFESTATIONS

Esophagus

Esophageal ulceration and strictures constitute the major adverse GI manifestations of NSAID intake. The exact mechanism of injury is not clear. Prolonged mucosal contact leading to mucosal disruption and exposure of esophageal mucosa to gastric acid injury appear to be responsible for esophageal mucosal injury.⁹ The diagnosis is made after excluding other common causes such as reflux disease, other drugs and infections. Strictures are less widely appreciated, and are suspected especially when endoscopically the mucosa appears to be healthier than that seen in reflux-related stricture.

Stomach

Gastro-duodenal lesions developing from NSAID use may not always be symptomatic. Endoscopic evidence of gastric ulcer occurs in 10% to 40% of individuals taking NSAIDs, and duodenal ulcer is reported to occur in 4% to 15% in the first 3 months of use.^{10,11} Certain factors, like prior peptic ulcer disease and NSAID-related GI complication, advanced age, concomitant use or glucocorticoids or anticoagulants, high or multiple doses of NSAIDs, ethanol use, and presence of co-morbid illness are definitive risk factors; *Helicobacter pylori* and smoking are possible risk factors.

The association between *Helicobacter pylori* and NSAID use in the causation of gastro-duodenal injury is interesting with regard to symptom profile, anatomic location, histological features and recurrence pattern. Ulcers caused by *H. pylori* are more often duodenal, recur after treatment if infection is not eradicated, and are often associated with dyspepsia and histological evidence

of chronic gastritis. In contrast, NSAID-induced ulcers are more often gastric in location, are generally asymptomatic, not associated with histological evidence of gastritis, and never recur once the causative drug is withdrawn. Whether their coexistence augments or attenuates GI injury is yet unknown.

Small intestine

NSAIDs cause small bowel mucosal damage in the form of strictures, diaphragms, enteropathy and serious complications such as perforation. The exact mechanism of small bowel damage is not known, but increased intestinal permeability, mucosal disruption and bacterial invasion causing blood and protein loss are some proposed mechanisms.

Autopsy studies provide useful information about small bowel injury due to NSAIDs. One such study showed the prevalence of small intestine ulcers to be 8.3% in the NSAID-consuming population with rheumatoid arthritis vs. 0.6% in the control population.¹² Diaphragms in the small intestine are less common, a retrospective study showing their occurrence in up to 1.5% of users.¹³

The term small bowel enteropathy is used to describe diffuse intestinal inflammation and increased intestinal permeability. It includes a whole range of entities such as chronic GI blood loss, protein-losing enteropathy, iron deficiency anemia, nutrient malabsorption, and fecal occult blood positivity.¹⁴ Blood loss is by far the commonest symptom.

This part of the intestine is relatively inaccessible to endoscopy and radiological investigations are not very useful in diagnosis. Diaphragms are better palpated on exploration or better appreciated on distended bowel during imaging. Permeability studies using chromium-labeled EDTA show elevated urinary levels of ⁵¹Cr EDTA within 12 hours of NSAID consumption and normalization within 4 hours of stoppage of NSAIDs. Indium-labeled neutrophil scintigraphy shows positive scans in almost 50% of NSAID consumers where the labeled neutrophils localize to the inflamed portion of small intestine demonstrating the increased inflammation of small bowel in NSAID users. Fecal excretion of this indium is increased and is used as a sensitive and quantitative index to document gastrointestinal inflammation.

A majority of lesions are asymptomatic and so do not require treatment. Symptomatic strictures, diaphragms and perforations require surgical correction. Stoppage of the drug is beneficial in patients with chronic GI blood loss when NSAIDs are suspected to be the cause. Protein loss can be prevented by the use of namebutone; co-administration of metronidazole reduces GI permeability changes. Later supports the theory of bacterial inflammation as a contributing factor to NSAID-related intestinal injury.

Colon

Colonic injury among NSAID users is less appreciated and diagnosed. Animal studies suggest fewer instances of colonic lesions as compared to gastro-duodenal ones.

The right colon, especially the cecum, is the prime site of colonic ulceration. Diclofenac rectal suppositories have been reported to be linked with lower GI bleeding and colonic perforation.¹⁵ A higher prevalence of strictures and diaphragms is known.

Colitis is frequently segmental, non-specific on histology, and is characterized by variable manifestations. Occasionally, histology may show features suggesting eosinophilic infiltration or collagenous changes.

Anorectal diseases are generally seen with local use in the form of suppositories and may result in symptoms such as proctalgia, tenesmus, or watery diarrhea. Local pathology may vary from proctitis to ulcers and anorectal strictures.

Patients with pre-existing colonic disease may have worsening of symptoms on NSAID intake. Both ulcerative colitis and diverticular disease are known to exacerbate during NSAID use.^{16,17} It is not known whether treatment with COX 2 inhibitor leads to less adverse effects as compared to non-selective NSAIDs.

Discontinuation of the drug results in recovery within 3 weeks. Balloon dilation is a convenient modality to treat colonic strictures and surgery can be reserved for resistant cases.

MANAGEMENT OF NSAID-RELATED GASTRO-DUODENAL INJURY

Various factors influence the treatment and prevention of gastro-duodenal ulcers in persons using NSAIDs. These include the type, dose and duration of the drug chosen; concomitant medication with specific reference to steroids, warfarin and aspirin; age of the patient, and prior complicated or uncomplicated GI events.

Prevention

Histamine H₂ receptor antagonists are not useful in the prevention of NSAID-related stomach injury. Misoprostol, a prostaglandin analogue, has been studied for its efficacy to protect gastric mucosa from NSAID damage; it appears to be cost-effective in only a subgroup that is at high risk for NSAID-induced ulcers. Proton pump blockers are more effective in prevention of GI ulcers.

Treatment

Prospective randomized trials (CLASS and VIGOR)¹¹ comparing the safety of aspirin and selective and non-selective NSAIDs have shown the following results. In chronic aspirin users, the use of celecoxib was found to give similar rate of symptomatic GI events when compared to ibuprofen, though there were fewer symptomatic GI ulcerations in celecoxib users. Among aspirin non-users, celecoxib had significantly lower incidence of both symptomatic and complicated GI events. Also, importantly, the addition of celecoxib or other traditional NSAIDs (ibuprofen or diclofenac) to existing aspirin consumption did not raise the incidence of symptomatic complicated GI events.

The VIGOR study addressed the issue of COX 2 inhibitor-related increased incidence of cardiovascular side effects due to its uninhibited increase of platelet aggregation. This was found to be higher in celecoxib users. The relative safety of COX 2 inhibitors over older NSAIDs is still controversial.

The administration of a nitric oxide (NO)-releasing derivative of naproxen to arthritic rats gave significantly reduced incidence of GI mucosal events when compared to aspirin, naproxen and celecoxib. This study also documented cellular events during inflammation, such as elevated levels of IL-10, increased gastric

COX 2 secretion, including that of mRNA protein, and gastric PGE₂ synthesis. Aspirin not only reduced inflammatory mediators but also caused significantly higher GI injuries. Celecoxib was able to reduce PGE₂ and aspirin-triggered lipoxin. This is a pro-inflammatory mediator regulating neutrophil endothelium interface reactions. NO-releasing naproxen not only reduced pro-inflammatory mediators, it also reduced neutrophil adherence to endothelium, suggesting its potential as a safer analgesic with better safety profile.

Nitric oxide (NO)-releasing naproxen (HCT-3012) interactions with aspirin in gastric mucosa of arthritic rats reveal a role for aspirin-triggered lipoxin, prostaglandins and NO in gastric protection.

A human study¹⁹ supporting these findings has recently shown benefit of NO-releasing NSAIDs. COX-inhibiting nitric oxide donors (CINODs) are probably candidates as future NSAIDs that may provide adequate control of inflammation, fewer GI adverse effects, and better profile for neutrophil-endothelial reactions.

GUIDELINES FOR APPROPRIATE USE OF NSAIDS

Two recent reviews have provided guidelines for the use of NSAIDs, their safety, drug interactions, adverse effects and preventive measures.^{20,21}

A few of the conclusions are:

1. In patients below age 65 with no prior drug consumption and GI event, NSAIDs can be given alone, but they need to be combined with a proton pump inhibitor if the patient is either on aspirin or has had a prior GI event.
2. COX 2 inhibitors can be instituted alone if either aspirin consumption or GI event alone is present, but need co-administration of a proton pump inhibitor if both of these are present or the patient needs steroids or warfarin in addition.
3. In patients above the age of 65 with or without prior GI event, NSAIDs alone are inappropriate; these patients need a proton pump inhibitor supplementation. In patients with no risk factor such as prior use of aspirin, steroid or warfarin intake, COX 2 alone may be used, but the presence of any one of them necessitates simultaneous use of a proton pump inhibitor. Thus, age above 65, prior GI event (complicated or uncomplicated), prior ingestion of any one of aspirin, steroid or warfarin, preclude the use of NSAIDs alone; these should always be given with a proton pump inhibitor. COX 2 alone or in combination with a proton pump inhibitor is a better choice in these situations.
4. Misoprostol significantly reduces adverse effects of non-selective NSAIDs. H₂ receptor antagonists cannot be used to prevent or treat NSAID-related GI injury.

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