Non-Steroidal Drug-induced Gastrointestinal Toxicity: Mechanisms And Management
Vikas Dhikav*, Sindhu Singh**, Swati Pande***, Atul Chawla****, Kuljeet Singh Anand*****

Abstract
Non-steroidal anti-inflammatory drugs are among the most frequently prescribed drugs worldwide. Because of their ‘over-the-counter’ (OTC) availability, they are also consumed on non-prescription basis as well. Though reasonably safe in most cases in prescribed dosages and for short durations, these drugs cause gastrointestinal toxicity in a large number of cases. They can affect all segments of the gastrointestinal tract. In the mouth, they cause oral ulceration, in oesophagus, they can cause ulceration and stricture formation. In stomach and duodenum, they can cause ulcers, severe bleeding, perforation, and obstruction. Most cases of NSAID-induced gastrointestinal ulcers can heal spontaneously, even when the drug is continued. However, in some they can cause serious toxicity requiring hospital admission and aggressive management. Considering the large number of people using these drugs on a daily basis, even if these side effects occur in a small percentage of cases, this translates into a large figure. It is therefore imperative for physicians to be aware about the serious adverse effects associated with them, and use these drugs only when genuinely indicated. Self-medication or indiscriminate use of these drugs as analgesics should be discouraged. Lowest dose of the safe NSAIDs like ibuprofen and diclofenac should be used for shortest possible duration. Once the ulcers develop, they should be treated with proton pump inhibitors such as omeprazole. Prophylactic use of H2 blockers, or antacids is without benefit and is not recommended. However, proton pump inhibitors can also be used prophylactically, especially those at risk of serious toxicity. In such cases, and in those who can afford, cyclooxygenase-2 selective drugs such as celecoxib and rofecoxib can be used. Newer agents like licofelone represent an attractive option.

Introduction
The gastrointestinal tract (GIT) is the main target of NSAID toxicity. It is the most frequent organ affected by adverse drug reactions in the USA. Unfortunately, it is also the most common drug-induced toxicity that can be fatal. World over, 35 million people consume these drugs on a daily basis, and about 30% of these users may develop GI toxicity of sufficient degree requiring a physician’s intervention. It has also been estimated that one third of the cost of treating arthritis patients relates to treatment of the side effects of NSAIDs. Conservative calculations estimate that approximately 1,07,000 patients are hospitalised annually for non-steroidal anti-inflammatory drug (NSAID)-related gastrointestinal (GI) complications, and at least 16,500 NSAID-related deaths occur each year among arthritis patients alone. The figures for all NSAID users would be overwhelming. Surprisingly, the management of this problem has undergone little change in the past 50 years, and is not only frequently under-diagnosed but also under-treated. Indian studies have shown that NSAIDs are among the most common drugs responsible for adverse drug reactions seen in clinical practice. In general, at least 10 to 20 percent of patients have dyspepsia while taking an NSAID, although the prevalence may range from 5 to 50 percent. Within a six-month period of treatment, 5 to 15 percent of patients with rheumatoid arthritis can be expected to discontinue NSAID therapy because of dyspepsia. Incidence of new ulcers range from 10-40% for gastric ulcers and 5-15% for duodenal ulcers. Most patients are, however, asymptomatic. According to prospective data from the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS), 13 of every 1,000 patients with rheumatoid arthritis who take NSAIDs for one year have a serious gastrointestinal complication. The risk in patients with osteoarthritis is somewhat lower (7.3 per 1,000 patients per year).

Mechanisms of NSAIDs-induced GI ulcerations
What causes ulceration is precisely not known. It is believed to occur as the result of a complex interplay of aggravating factors and protective factors. Prostaglandins...
(PGs) have long been known to be mucoprotective and ulcer healing agents. Prostaglandins protect GI mucosa by forming a cytoprotective layer and increasing the secretion of bicarbonate ions that neutralise the gastric acidity. All therapeutically useful NSAIDs act by inhibiting the synthesis of PGs. Cyclooxygenase has two isoforms, one constitutive (COX-1) and another inducible (COX-2). A third isoform (COX-3) has recently been described as well. NSAIDs are now divided into selective (those inhibiting COX-2) and non-selective (inhibiting both COX-1 and COX-2). Conventional NSAIDs cause non-selective inhibition of cyclooxygenase, which leads to reduction in bicarbonate secretion and reduced mucous production. Coupled with it is vasoconstriction that occurs due to NSAIDs, which causes hypoxia and consequent formation of ulcer. Most NSAIDs are weak organic acids and have low pKa. Therefore, they remain unionised in stomach and are absorbed appreciably from stomach. However, once they breach the cell membranes of stomach cells and reach within, they encounter a basic pH (e.g., 7.1). This causes so called “trapping” of the drugs inside the cell. This topical effect is considered an important mechanism of gastro-duodenal damage associated with their use. Even short-term (< 1 week) use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) can precipitate ulcer-related bleeding. Risk of ulcer development is increased in patients with advanced age, positive family history, female sex, prolonged use of high dose of NSAIDs and concomitant use of other gastrotoxic or anticoagulant drugs, alcoholism, heavy coffee consumption, and poor general health. Role of H. pylori in the development of NSAID-induced ulcer is not entirely clear. Thus, it can be understood to be the disease of the war between the factors favouring and those opposing the development of ulcers where the former win over the latter. Although NSAID use is primarily associated with upper GI problems, it is also associated with lower gastrointestinal symptoms such as haemorrhage, inflammation, perforation, and stricture formation. ARAMIS data suggested that risk of death from NSAID use is four times more than non-users. Over-the-counter (OTC) availability of histamine H2 receptor antagonists for short-term treatment of dyspepsia may lead a patient to delay optimal care for more severe gastrointestinal disease; if the drug is taken on a long-term basis, its use could delay a diagnosis of gastric cancer also.

Recent studies have shown that use of multiple NSAIDs; non-use of anti-ulcer medication, and NSAID use in patients with previous history of peptic ulcers raises the possibility of developing GI ulcers by 14-17 folds. Even aspirin use for prophylactic reasons in low dosages is not free of gastrointestinal complications. A large study including over 1,000 patients in five large hospitals of England has suggested that all conventionally used regimens of aspirin can cause ulcers. All formulations of aspirin like buffered, enteric coated, and plain aspirin carry same amount of risk. Elderly patients are particularly prone to develop GI toxicity and unfortunately they are the most frequent users of this group of drugs. These patients are deficient in cytoprotective PGs (PGE2 and PGI2) that increase mucous production and improve ulcer healing. Moreover, the vascular integrity of the ulcer base is poor; therefore, ulcers bleed easily. Many more predisposing factors have been identified. These are summarised in table-I.

Table I : Predisposing factors for NSAID induced GI ulceration.

<table>
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<th>Factor</th>
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<tr>
<td>Previous history or active peptic ulceration</td>
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<tr>
<td>Advanced age (&gt; 65)</td>
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<td>Female gender</td>
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<tr>
<td>Smoking, alcoholism</td>
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<tr>
<td>Heavy coffee consumption</td>
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<tr>
<td>Concomitant ingestion of GI toxic drugs (e.g., steroids)</td>
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<tr>
<td>Prolonged use of heavy doses of NSAIDs</td>
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<tr>
<td>Use of multiple NSAIDs; concomitant administration of anticoagulant</td>
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<tr>
<td>Hepatic-renal dysfunction</td>
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<td>Serious systemic illness</td>
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Table II : NSAID ingestion and GI injury.

<table>
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<tr>
<th>Injury type</th>
<th>Gastro-duodenal lesion</th>
<th>Frequency</th>
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<tr>
<td>Acute (1-2 weeks)</td>
<td>mucosal erythema, superficial erosions, submucosal haemorrhage, increased faecal blood loss</td>
<td>60-100%</td>
</tr>
<tr>
<td>Chronic (&gt; 4 weeks)</td>
<td>gastric antral erosions and ulcers, duodenal ulcers and erosions</td>
<td>5-30%</td>
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Clinical features

NSAID induced GI damage is of three main types:

a) Superficial damage such as mucosal haemorrhages
and erosions.
b) endoscopically documented non-symptomatic ('silent') ulcers
c) symptomatic ulcers causing complications such as GI haemorrhage.

**Table III: Prevention of NSAID induced ulcers.**

<table>
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<tr>
<th>Prevention Measures</th>
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<tr>
<td>Use single NSAID</td>
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<tr>
<td>Use the lowest possible doses</td>
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<tr>
<td>Use for short durations</td>
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<tr>
<td>Use less gastrotoxic drugs like paracetamol, ibuprofen, and diclofenac</td>
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<tr>
<td>Use selective COX-2 inhibitors wherever possible and especially in high risk cases</td>
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<tr>
<td>Review drug use in elderly</td>
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<tr>
<td>Avoid concomitant gastrotoxic drugs like steroids</td>
</tr>
<tr>
<td>Consider prophylaxis with omeprazole in high risk cases</td>
</tr>
<tr>
<td>Have a high index of suspicion on GI symptoms in NSAID users</td>
</tr>
<tr>
<td>Educate patients against non-prescription use; counsel them about the warning symptoms of GI damage such as blood stained stools, blood in vomitus, and melena, etc.</td>
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Ulcers are usually symptomless unless complicated. Early symptoms are mild and benign like dyspepsia, nausea, vomiting, and anorexia. Pain is usually a late feature. Moreover, it is not usually possible to diagnose these ulcers on the basis of clinical features alone, as symptoms suggestive of the ulcers can occur frequently in their absence. Elderly patients usually have painless gastric ulceration and NSAIDs can mask the symptom of pain. In fact, most elderly patients are referred to physicians for iron deficiency due to faecal blood loss and not because of the ulcers-induced pain. Few features, however, can be suggestive of NSAID-induced ulceration – like absence of *H. pylori* infection, anorexia rather than abdominal pain, antral location of gastric ulcers, known risk factors, and prolonged self-medication of the large doses of NSAIDs.

Chronic NSAID use can increase the risk of ulcer development by 10-30 folds. It is noteworthy that aspirin use even for conditions such as cardiovascular prophylaxis causes substantial GI toxicity. Patients may also present with iron deficiency anaemia as chronic use of aspirin can cause up to two litres of the blood loss. Type of NSAID injury and the objective way to assess it is given below in table IV and V. Apart from gastrotoxicity, NSAIDs can affect virtually all segments of GI tract.

**Table IV: Features of NSAID induced problem ulcers.**

<table>
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<th>Features</th>
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<tr>
<td>More than 3 mm in size</td>
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<tr>
<td>Deep lesions</td>
</tr>
<tr>
<td>Prone to complications like bleeding, perforation, and obstruction</td>
</tr>
<tr>
<td>Gastric or duodenal in location</td>
</tr>
<tr>
<td>Multiple erosions (more than 10)</td>
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<tr>
<td>Antral in location</td>
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**Oesophagus**

Principal manifestations of oesophageal involvement are ulceration and strictures; aspirin is thought to disrupt oesophageal mucosa, thus exposing it to deleterious effects of acid. Prolonged contact with most NSAIDs can result in ulceration due to caustic properties. They can result in oesophagitis and even strictures. Both are, however, more commonly caused by reflux rather than NSAIDs.

**Small intestine**

Ulceration of small intestines has historically been difficult to study. One endoscopic study found a prevalence of 26% in patients taking these drugs on long-term basis and presenting as cases of occult blood loss. In small intestine, serious lower GI events occurred at a rate of 0.9% per year in rheumatoid arthritis patients taking non-selective NSAIDs; accounting for 40% of the total adverse GI events in these cases. In patients taking COX-2 inhibitors, events were less by 54%, signifying that these drugs were half as likely to cause adverse GI events as compared to conventional drug. A number of studies suggest that perforation in small intestine is related to slow-release formulations of NSAIDs. Another
autopsy study showed that small intestinal ulcers have developed in 8.4% patients as compared to 0.6% of control group. Syndrome of occult blood loss, malabsorption, anaemia, and protein losing enteropathy has been described in many cases.

**Large intestine, rectum, and anal area**

There are only a few cases of NSAID induced damage in this segment of GIT. Antibody-induced prostaglandin depletion produces substantial damage in stomach and duodenum as compared to colon. In colon and ano-rectal area they cause colitis, proctitis, presentation similar to inflammatory bowel disease, bleeding (both acute and chronic), ulcers, and strictures. Most ulcerative complications like perforation are seen in caecum. All classes of NSAIDs, including aspirin at low dosages (325mg/day) were shown to cause them. Rectal suppositories can result in proctalgia, tenesmus, or watery diarrhoea. Approximately, 10-30% cases can develop these problems.

Arthritis, rheumatism, and ageing medical information system (ARAMIS) post-marketing surveillance programme (PMS) has prospectively followed patient status and outcomes, drug side effects, and the economic impact of illness for > 11,000 arthritis patients at 8 participating institutions in the United States and Canada. Analysis of these data indicates that: (1) osteoarthritis (OA) and rheumatoid arthritis (RA) patients are 2.5-5.5 times more likely than the general population to be hospitalised for NSAID-related GI events; (2) the absolute risk for serious NSAID-related GI toxicity remains constant and the cumulative risk increases over time; (3) there are no reliable warning signals (> 80% of patients with serious GI complications had no prior GI symptoms); (4) independent risk factors for serious GI events were age, prednisalone use, NSAID dose, disability level, and previous NSAID-induced GI symptoms; and (5) antacids and H2 antagonists do not prevent NSAID-induced gastric ulcers, and high-risk NSAID users who take gastro-protective drugs are more likely to have serious GI complications than patients not taking such medications. Currently, limiting NSAID use is the only way to decrease the risk of NSAID-related GI events.

**Management of the GI injury**

**Prevention of the ulcer**

It is noteworthy that most of the gastrointestinal lesions heal even with continued use of drugs. That is self-regeneration or self-renewal process within the body. Some, however, develop serious lesions requiring clinical attention. Removal of the aggravating factors, like smoking, alcohol, and coffee consumption should be sought. Ulcer prophylaxis should be considered in the patients who are taking NSAIDs, but continue to smoke or use alcohol. Those patients who have ulcers but are not taking NSAIDs should receive antiulcer drugs like H2 blockers, e.g., famotidine or ranitidine. Early diagnosis and treatment of GI ulcers should be emphasised to prevent this problem to a large extent.

Diagnosis of the NSAID induced ulcers is mainly based upon clinical suspicion and more frequent upper GI endoscopies are recommended in these patients. Ulcer base during endoscopy should be biopsied and histological and biochemical investigations like catalase, urea breath test, and serological evaluation should be done to know the presence of H pylori in the specimen. A new investigative test to know the platelet COX levels is under evaluation. Studies have shown that if NSAIDs are taken for short duration and in low doses, then they are relatively safe for GI tract. Less gastrotoxic drugs like ibuprofen and diclofenac should be used for long-term treatment of inflammatory joint disease.

Proper precautions should be taken for prevention of ulcers. A large study involving 421 patients admitted to the hospital with upper gastrointestinal haemorrhage, who took NSAIDs revealed that non-prescription drug use was an important cause of bleed. The most common sites of bleeding in this study were gastric ulcers (31 per cent) and duodenal ulcers (26 per cent). About 35 per cent of the patients had taken over-the-counter aspirin while another six per cent had taken prescription aspirin. Another 20 per cent of the patients had taken NSAIDs other than aspirin either by prescription or bought over-the-counter. Therefore, attempts should be made to discourage people from taking these drugs on non-prescription basis, especially over a long term without clinical supervision. Concomitant use of H2 blockers has failed to show acceptable protection. Two large studies of
patients with duodenal ulcers have not given encouraging results. Misoprostol given together with NSAIDs has shown acceptable degree of protection, with a reduction in the number of gastric or duodenal lesions in studies lasting for 6-12 months duration. Proton pump inhibitors such as lansoprazole are superior to placebo for the prevention of NSAID-induced gastric ulcers but not superior to misoprostol, 800 µg/d. When the poor compliance and potential adverse effects associated with misoprostol are considered, out of proton pump inhibitors and full-dose misoprostol, the former is preferred clinically.

One study showed that frequency of serious events like bleeding and perforations were less, bleeding reduced by 40% and overall reduction was 60-70%. However, the side effects like diarrhoea were the limiting factors. Several randomised trials have shown that the proton pump inhibitor drugs such as omeprazole are effective in reducing gastrointestinal damage caused by NSAIDs if they are given prophylactically. Two large placebo control studies have shown that omeprazole 20 mg/daily reduced incidence by 71% and 78% over 3-6 months in respective studies. These studies named OMNIUM and ASTRONAUT have investigated over 1,000 cases. These investigated omeprazole 20 mg with ranitidine 150 mg and placebo. Most patients selected were high-risk cases as they either had a past history of ulcer, or were having ulcer and were taking drugs as well. Omeprazole reduced the chances of getting ulcers by 70-75% compared with placebo. Other PPIs have not been investigated. Early results show that lansoprazole also exhibits similar protection. Risk of serious gastrointestinal damage was found to be higher in rheumatoid arthritis patients taking NSAIDs with some prophylactic agents such as H2 blocker or antacids than those who were taking them alone. Although exact reason is unknown, it could possibly be due to the fact that these drugs mask the symptoms of gastric damage such as dyspepsia or pain. In misoprostol ulcer complications outcome safety assessment (MUCOSA) study, concomitant treatment with misoprostol achieved a reduction in adverse gastrointestinal events by 40% as compared to placebo. There are, however, no published guidelines as to which patients should receive prophylaxis. A recent endoscopic study compared ranitidine and omeprazole for ulcer prophylaxis in patients in whom NSAID could not be discontinued. After 6 months of treatment, 16.3% patients had gastric ulcers and 4.2% had duodenal ulcers. In omeprazole group, 5.2% had gastric ulcers, and only 0.5% had duodenal ulcers. It is apparent from this data that ranitidine is effective only in reducing frequency of duodenal ulcers, but that is below the acceptable standard for a prophylactic agent. Therefore, their use for ulcer prophylaxis in high-risk cases cannot be recommended.

**Healing of the established ulcer**

Treatment of the GI ulceration is challenging. Attempt should be made to prevent it from developing. Drug discontinuation is the most obvious option but may not always bring relief as symptoms can persist even after one year of the drug discontinuation. Moreover, drug discontinuation may not be feasible in all patients as the dangers of drug discontinuation can be considerable – like pain and stiffness. For patients with non-inflammatory joint disease like osteoarthritis (OA), non-pharmacological options like weight reduction, exercise, and physiotherapy should be tried. Recent evidence suggests that drugs with less potential for GI irritation like paracetamol should be introduced early in the course of the disease. Indeed, paracetamol is presently the frontline drug in patients with symptomatic OA. Individual NSAIDs also differ in their propensity to cause ulceration but none is free from causing the risk of ulcer when taken on a long-term basis. Newer NSAIDs like celecoxib have shown to have a fourfold lesser potential for causing ulceration. An important deterrent with their routine use is that they are quite expensive. Celecoxib for example is 35 times more costly than aspirin – and nearly 10 times than ibuprofen. Studies have shown that 40 mg daily ingestion of famotidine for 8-12 weeks brings ulcer healing in more than 90% of the cases. Many studies have examined the comparative efficacy of famotidine and ranitidine and have found it to be equal in both cases. Patients with GI ulcers requiring NSAIDs can be given misoprostol, a prostaglandin E1 analogue in a dose of 100 micrograms four times daily; or a PPI, 20 mg daily. Diarrhoea occurs with this dose in a small number of patients, but the incidence is less as compared to 200 microgram daily doses. Proton pump inhibitors such as lansoprazole are superior to placebo for the prevention of NSAID-induced gastric ulcers, but not superior to misoprostol, 800 µg/d. Role of misoprostol in the situations where low dose aspirin is used is not clear,
but probably it is not required. However, recent evidence shows that healing rates with H2 blockers would be suboptimal – only about 70% ulcers will heal inspite of patients continuing to take these drugs. Recent ASTRONAUT study\(^{20}\) showed that omeprazole (20 mg/daily) produces better healing rate than misoprostol 200 \(\mu\)g four times daily or 150 mg/day of ranitidine. Other H2-blockers do not seem to make any difference. We should, therefore, remember that the use of over-the-counter NSAIDs might be a more important cause of gastrointestinal bleeding than previously thought. Most cases of lower GI injury heal in about three weeks, once the offending drug is stopped. In cases of strictures, serial dilation may be needed.

**Cyclooxygenase-2 selective inhibitors**

Advent of COX-2 selective inhibitors is probably the most significant therapeutic advance after Vane’s epoch making discovery of mechanism of action of NSAIDs in 1971. Non-selective or conventional NSAIDs act by inhibiting both isoforms, while COX-2 selectively inhibit COX-2 only, in therapeutic dosages. Several such “coxibs” are: celecoxib, rofecoxib, and valdacoixib\(^{22}\). Several preferential COX-2 inhibitors, such as meloxicam, etodolac, nimesuline, and nabumetone are also available. Celecoxib and rofecoxib have especially become popular among clinicians. COX-2 inhibitors have been developed with the contention that inhibition of constitutive COX-1 by non-selective NSAIDs is responsible for the side effects such as ulcer and bleed. Therefore, drugs that spare this isoform should be free from these side effects. Short-term and long-term studies of patients taking these drugs have confirmed this notion. Incidence of serious side effects has been found to be comparable to placebo, while the incidence is 20-40% with conventional non-selective drugs. Two main prospective trials of COX-2 inhibitors involving about 8,000 patients each such as celecoxib and rofecoxib long-term arthritis safety study (CLASS) and VIGOR (vioxx gastrointestinal outcome research study) suggest that these have superior tolerability, safety, and in some cases efficacy as well over conventional NSAIDs.

**Future directions**

Increasing use of NSAIDs and with many upcoming uses like prevention of malignancies, stroke, pre-eclampsia, Alzheimer’s disease, and many other illnesses, it is imperative that these drugs are made safer and more tolerable. Development of COX-2 selective inhibitors is an important therapeutic advance in this regard, but they too are not entirely free from the problem of GI ulceration. Preventive strategies like use of PPIs or misoprostol are a welcome move, but it mandates the use of a 2nd drug. Moreover, PPIs can reduce NSAID absorption from GI tract; they can reduce the gastric acid output to almost nil. Therefore, newer ways to modify the drugs have been developed.

1. **Nitro-aspirins (NO-aspirins)**

Nitric oxide shares most of the muco-protective properties of prostaglandins. Therefore, several NSAIDs like flurbiprofen, naproxan, and diclofenac have been combined with nitric oxide moiety like glyceryltrinitrate or S-nitroglutathione. In experimental models, these have shown markedly reduced gastrototoxicity\(^{23}\).

2. **Zwitterionic phospholipids**

The rationale of combining NSAIDs with phospholipids is that the combination prevents the interaction of hydrophobic portion of cells to the drugs. This can help in reducing damage. One such combination of acetylsalicylic acid and dipalmitophosphatidylcholine retains analgesic and anti-inflammatory effects while exhibiting more antipyretic effects. Its tendency to cause GI damage is substantially reduced\(^{24}\).

3. **Chiral NSAIDs**

Attempts are being made to purify some of the commonly used drugs such as ibuprofen that exist as racemic mixtures. This is done following realisation that GI damage is caused by one of the isoforms, while the other one is safer\(^{25}\). Experiments in mice show that the S isoform leads to usual mucosal damage, while R has substantially less propensity to do so.

4. **Trefoil peptides**

These are a family of cysteine-containing protective peptides normally secreted in GI tract.
administration of these peptides has been shown to abrogate the GI damage produced by indomethacin.

A newer non-steroidal drug with novel mechanism of action: locofelone

Locofelone is a dual action, competitive, COX-2 cyclooxygenase and 5-lipoxygenase blocker. The rationale of its development represents the simple application of pharmacological principles in therapeutics. It is well known that cyclooxygenase enzyme has two isoforms upon which NSAIDs act, i.e., COX-1 and COX-2. Conventional NSAIDs and COX-2 selective inhibitors act mainly on COX-2. Blockade of COX-2 enzyme by COX-2 inhibitors leaves the COX-1 isoform unchecked and this contributes to enhanced thrombogenicity. Blockade of both COX-1 and COX-2 leads to increased formation of products of 5-lipoxygenase pathways and hence gastric damage. Locofelone acts to inhibit both isoforms (COX-1, COX-2) and 5-lipoxygenase. Its improved safety profile compared to other NSAIDs is believed to be due to its unique mechanism of action.

Conclusion

Non-steroidal anti-inflammatory drugs induced gastrointestinal toxicity is common and is frequently associated with adverse effects, which many a times are serious – like haemorrhage, perforation, and obstruction. NSAIDs affect all segments of GI tract, but stomach and duodenum are the worst affected areas. Management of NSAID related toxicity has undergone little change in the last half century. However, it is preventable in a large number of cases. Use small doses of the drugs for shortest possible duration, avoid prescribing antacids or H2 blockers like ranitidine, etc., for prevention, and consider ulcer prophylaxis in high-risk groups. Use of proton pump inhibitors such as omeprazole has been shown to be useful for both prophylaxis and treatment of an established ulcer. Misoprostol is helpful, but is expensive, not generally available, and is associated with diarrhoea. Wherever possible, and especially in those at risk, use of COX-2 selective drugs like celecoxib are recommended. With the advent of many experimental strategies to abrogate the toxicity and emergence of drug with novel mechanism like locofelone, the incidence of this serious toxicity can possibly be reduced to a considerable extent in future.

References


