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COMPARATIVE REVIEW OF ANTISECRETORY & MUCOSAL PROTECTIVE DRUGS FOR NSAID RELATED GI COMPLICATIONS

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ABSTRACT

Non-steroidal anti-inflammatory drugs have been used most widely in many diseases. Despite of many therapeutic effects the use of NSAIDs has also been associated with cardiovascular (CV), renal, and gastrointestinal (GI) complications. In which GI complications are most common. GI complications are generally mediated through inhibition of mucosal cyclooxygenase-1 (COX-1) primarily and suppression of prostaglandin production. According to literature H. pylori and NSAIDs are the two most common causes of peptic ulceration. Many agents have been used in treatment and prophylaxis of GI complications such as mucosal protective agents, antisecretory drugs, antibiotics and probiotics, food constituent etc. Majorly used drugs for NSAIDs related GI complications are PPIs, H_2RA and misoprostol. In this article a comparison has been made between these three categories of drugs. This article also covers the comparison on the basis of cost, pregnancy etc. As per review it can be concluded that PPIs are superior then H_2RA and Misoprostol because of high efficacy in ulcer treatment, Long lasting effect of drug, potency, healing ulcer also in case of continuous NSAID therapy. Although PPIs are more effective than H_2RAs, some patients can be switched to H_2RAs are remain satisfied with their treatment.

KEYWORDS: Gastrointestinal complications, antisecretory drugs, food constituent, PPIs, H_2RA, misoprostol.

INTRODUCTION

Non-steroidal anti-inflammatory drugs are widely accepted for controlling pain despite of this their administration may lead to the initiation of many gastrointestinal complications, e.g., ulcers and erosions, in many individuals. It has been reviewed that the major factor contributing the development of these complications are the acid present in the stomach and upper small intestine. There are many other factors contributing to NSAID-associated gastric complications such as a toxic effect of NSAIDs and prostaglandins inhibition. This can also enhance the possibility of many patients to become more susceptible to the ulcerogenic effects of many other stimuli.[1]

The mechanism of action of NSAIDs describes that they act by inhibiting an enzyme called cyclooxygenase (COX). The COX enzyme has two forms known as COX-1 and COX-2. COX-1 is an enzyme that produces a product that helps protect the lining of the stomach, and COX-2 is involved in the process of inflammation. Hence, when NSAIDs are given to the patient, they reduce inflammation but, at the same time, inhibit an enzyme which is responsible for protecting the lining of the stomach. As a result, NSAIDs are associated with ulcers and gastro-intestinal bleeding. So NSAIDs are effective for a number of conditions but side effects associated with their use limits their usefulness, particularly in case of long term use.[2]

Many of useful pharmacologically active NSAIDs inhibit the synthesis of PGs4. Conventional NSAIDs cause non-selective inhibition of COX, by which there is a reduction in bicarbonate secretion and also reduction in mucous production. It is also reviewed that vasoconstriction that occurs due to NSAIDs, also causes hypoxia and consequent formation of ulcer.

Almost all NSAIDs are weak acids, having less pKa value. Therefore, they are absorbed mainly from stomach and are unionised in stomach. However, when they reach to the cell membranes of stomach and permeate within, they generate a basic pH (7.1). This causes “trapping” of the drugs. This topical effect is an important mechanism of gastrointestinal damage associated with NSAIDs. Even short-term use of some NSAIDs such as aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) can generates ulcer-related bleeding. [3]

NSAID RELATED GI COMPLICATIONS

NSAIDs use also been associated with many complications such as cardiovascular (CV), renal, and gastrointestinal (GI) complications, and certain patients are at increased risk of NSAIDs side effects. NSAIDs use also results in less but consistent increases in the risk of CV complications such as myocardial infarction, affected in part by dose and potency of cyclooxygenase-2 (COX-2) inhibition. NSAIDs use has also long been associated with kidney disease, resulting in both acute and chronic reduction in kidney function.[4]

GI complications are generally mediated through inhibition of mucosal cyclooxygenase-1 (COX-1) primarily and suppression of prostaglandin production. However, COX-2 inhibition and other mechanisms, like changes in the bacterial microbiome in the gut or the generation of free radicals, are also generally involved.[5]

It has been reviewed that H. pylori and NSAIDs are the two most common causes of peptic ulceration. In case of interactions of H pylori and NSAIDs no clear picture shown that can apply to all situations. In many cases, NSAIDs and H pylori have similar adverse effects on mucosal protective mechanisms, and despite H pylori itself producing small amounts of prostaglandins, there remains the possibility of an additional damaging effect when both are present. Studies on mucosal adaptation and on neutrophils raise the possibility of some inter-relationship that may allow damage to occur more readily when NSAIDs are taken in the presence of H pylori. The development of an ulcer when NSAIDs are given to patients who are H pylori positive may depend on the interaction of a number of factors, including previous exposure to NSAIDs, past history, gastric acid output, and the use of acid suppression drugs such as PPIs.[6]

The most common complications are bleeding and perforation present in the oesophagus, stomach, and duodenum due to NSAID effects on platelets and on a variety of mucosal wounds. Complications arise from primarily existing peptic ulcer, NSAID-induced ulcers and erosions, and other complications (not caused by the use of NSAIDs) caused to bleed by NSAID-induced platelet dysfunction. There is a confusing term "NSAID gastropathy" used to describe a variety of pathogenically distinct mucosal wounds. Failure to differentiate between the different forms of NSAID injury has encourage clinical investigation.[7]

Gastroduodenal or gastrointestinal ulceration and bleeding are the major limitations to the use of non-steroidal anti-inflammatory drugs (NSAIDs). The development of safer NSAIDs or of effective therapies for the prevention of the adverse effects of existing NSAIDs needs a better understanding of the pathogenesis of NSAID-induced ulcer disease. They can affect almost all parts of the gastrointestinal tract. In the mouth, they can cause oral ulceration, in oesophagus, they can cause ulceration and structure deformation. 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 hospitalization and immediate management.[8]

AGENTS USED FOR NSAID RELATED COMPLICATIONS

Use of less toxic COX-2 inhibitors

The search for a less gastrointestinal toxic NSAIDs led to the development of the COX-2 inhibitors. It had been well known that NSAIDs inhibited the enzyme cyclooxygenase (COX), leading to a significant decrease in prostaglandin production. COX exists in two isozymes, COX-1 and COX-2. COX-1 is a constitutive enzyme and exists in many body tissues, including the stomach, where it facilitates the production of those prostaglandins considered to be important in gastric mucosal protection. COX-2, on the other side, it is an inducible enzyme and is associated with inflammation in the joints. It was reported that the selective inhibition of COX-2 lead to decreased inflammation in musculoskeletal tissues and, by sparing COX-1, to a decrease in the incidence of GI mucosal injury.[9]

Use of Mucosal Protective Agents

It has already been reported that gastrointestinal side effects associated with NSAIDs are caused by a decrease in PGs level in the gastric mucosa. It has therefore been proposed that compensation for the reduction in mucosal PGs by administration of exogenous PGs may be able to minimize NSAID-induced gastric side effects. Of the many PG derivatives that have been synthesized to date, only misoprostol, a PGE1 derivative, is available commercially. Furthermore, compounds with different (i.e., non-PG) chemical structures but similar mucosal protective activity to PGs have been developed in Japan, and some of them are now used as anti-ulcer drugs in Japan and other Asian countries. Several recent pilot studies have revealed that some of these latter drugs, as well as misoprostol, are effective in limiting the GI side effects of aspirin and other NSAIDs.[10]

Use of Antisecretory Agents

Though antisecretory drugs such as PPIs and H_2-RAs are commonly used to prevent gastrointestinal complications induced by NSAIDs, they are generally not considered to be effective in mitigating NSAID-induced small intestinal lesions. However, it has been reported that some PPIs and H_2-RAs are able to prevent the formation of intestinal lesions induced by NSAIDs.[11]

Use of Antibiotics / probiotics

Numerous studies using various kinds of antibiotics and other drugs suggest that gram-negative enterobacteria such as E. coli play an important role in the formation of intestinal complications. The use of antibiotics for the prevention of NSAID-induced intestinal damage has

therefore been proposed. The protective activity of probiotics against NSAID-induced damage to the small intestine has also been reported. It is a known fact that enterobacteria shows a major role in the development of NSAID-induced small intestinal complications. In a research done by Robert and Asano it has been shown that small intestinal lesions do not occur in germ-free rats given high-dose indomethacin for 3 days, whereas intestinal perforation and death occurred in most of the conventional rats treated with indomethacin.

Effect of Food constituents

It has also been seen that the development of intestinal complications by NSAIDs in rats, cats, and dogs depends on the feeding conditions; i.e., when NSAIDs were administered under fasted conditions they did not cause any visible complications in the small intestine, but when NSAIDs were administered after feeding they caused marked lesions in the small intestine. These results suggest that food constituents may also influence the formation of intestinal lesions.[12]

EXAMPLES OF MOST COMMONLY USED AGENTS

Histamine Receptor Antagonists (H_2RAs)

Among NSAID users, histamine receptor antagonists (H_2RAs) are the most commonly used over-the-counter gastroprotective agents. In a research it has been reported that, controlled trials of H_2RAs for the prevention of NSAID-associated gastroduodenal ulcers, standard doses of H_2RAs reduced the incidence of duodenal ulcers but not that of gastric ulcers. Three randomized, placebo-controlled trials evaluated the incidence of endoscopically detected ulcers in NSAID users who were taking double doses of famotidine (40 mg twice daily); their results were inconsistent even though the trial designs were essentially identical. Write now, there is no such evidences to support the use of double doses of H_2RAs in high-risk NSAID users.[13]

Proton-pump Inhibitors

A report on trials showed that PPIs significantly reduce the risk of endoscopically detected duodenal and gastric ulcers, in long-term NSAID users. Although PPIs are often recommended as the gastroprotective agent of choice in high-risk patients, this recommendation is largely inferred from endoscopic studies performed in patients with a low-to-moderate risk. Just one, relatively small-scale, clinical outcome trial has assessed the efficacy of PPIs in high-risk NSAID users. In this study patients who were H. pylori-positive, had a recent history of NSAID-related ulcer bleeding and continued to use naproxen, 1 week of H. pylori eradication therapy was compared with long-term omeprazole use. Recurrent ulcer bleeding occurred at a rate of 37.6 events per 100 patient-years in the eradication-therapy group, compared with 8.8 events per 100 patient-years in the omeprazole group.[14]

Misoprostol

of all the gastroprotective agents, only full-dose misoprostol (200 µg four times daily) reduces the risk of NSAID-induced ulcer complications by 40%. Nevertheless, side effects (including abdominal cramps and diarrhoea) and the need for multiple daily doses render this drug unpopular. Endoscopic studies show that lower doses of misoprostol (400-600 µg daily) are well tolerated and effective, and a combined tablet of diclofenac 50 mg and misoprostol 200 µg has been made available to improve patient compliance. Since then, however, another study has shown that half-dose misoprostol (200 µg twice daily) does not prevent recurrent ulcer complications in high-risk patients with arthritis and a history of ulcer bleeding.[15]

COMPARISON

PPI-H_2RAs

As mentioned in AGA (American Gastroenterological Association) recent guidelines medical Position Statement on the management of GERD "for the treatment of patients with oesophageal GERD syndromes (healing esophagitis and symptomatic relief) PPIs are more effective than H_2RAs, which are more effective than placebo". All other recent consensus guidelines are in agreement among them with regards to the above statement.

As per the ACG (American College of Gastroenterology) Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease: "The OTC [over the counter] H_2RAs are particularly useful when taken prior to an activity that may potentially result in reflux symptoms (heavy meal or exercise in some patients). Many patients can predict when they are going to suffer from reflux and can premedicate with the OTC H_2RAs. Comparisons between OTC H_2RAs and antacids are limited. It has been suggested that antacids provide a more rapid response, but gastric pH begins to rise less than 30 min after taking a dose of H_2RA so this does not seem to be a major factor. The peak potency of OTC H_2RAs and antacids are similar, but the H_2RAs have a much longer duration of action (up to 10 h)".[16]

Both the two majorly used antiulcer drugs PPIs and H_2RAs were more effective than placebo in maintaining an establishment of esophagitis and in maintaining symptom relief. However, PPIs were more effective than H_2RAs in maintaining a remission of esophagitis and in maintaining symptom relief. On the other hand, there is also found to be statistically significant increase in headache with PPIs compare with H_2RAs. According to the Cochrane review "Healing doses of PPIs are more effective than all other therapies, although there is an increase in overall adverse effects compared to placebo, and headache occurrence compared to H_2RAs. H_2RAs prevent relapse more effectively than placebo, demonstrating a role for PPI-intolerant patients".[17]

H_2RA vs. PPI: Speed of onset of action

As per the above discussion, PPIs are superior to H_2RAs regarding the time required to achieve complete resolution of symptoms in GERD and regarding the time required to achieve healing of esophagitis. These time periods are in the order of days or weeks.

However, H_2RAs have a faster **onset** of effect on the symptoms of GERD and NYD, compared to PPIs. This time period is in the order of minutes or 1-2 hours. Of note, "onset of effect" (when a patient has a noticeable improvement in his/her symptoms) is different from "complete resolution of symptoms" (when a patient is completely symptom free, even from mild, not-bothersome symptoms).[18]

Khury *et al* showed in a research in healthy volunteers that postprandial oral ranitidine provided more rapid increase in gastric pH to > 3 and > 4 compared to postprandial oral omeprazole. [19] Dettmar *et al* showed in a report studying 4-hour pH in GERD patients that oral ranitidine was superior to oral omeprazole in reducing the acidity in the stomach and the esophagus. [20] Hedenstrom *et al* in a research found that assessed 4-hour pH in healthy volunteers, found that oral ranitidine and famotidine resulted in a fast and significant raise in the intragastric pH while oral omeprazole had no effect in the intragastric pH during the study period (4-h).[21] Pipkin *et al* concluded that, in GERD patients, oral ranitidine or famotidine had a faster onset of action compared to oral omeprazole or a lansoprazole: The H_2RAs achieved a significantly greater and more rapid rise in intragastric pH in the hour immediately after dosing and offered a faster relief of symptoms.[22]

This suggests that H_2RAs may be more effective than PPIs for on-demand treatment for episodic heartburn or episodic dyspepsia.

H_2RA vs. PPI: Timing of administration in relation to meals

PPIs are more effective when administered before a meal.[23] As Howden & Chey have reported "PPIs are best absorbed in the absence of food. Ingestion of food after a PPI stimulates parietal cell activity when blood levels of the PPI are increasing; this promotes uptake of the PPI by the parietal cells. Therefore, patients should be advised to take their PPI between 30 and 60 minutes before eating. For patients on a once-daily PPI, the best time to take it is about 30 to 60 minutes before breakfast."[24]

On the other hand, H_2RAs can be administered at any time in relation to the meals: Orr *et al*, in a research in healthy volunteers, found that the timing of oral ranitidine administration in relation to a meal did not result in differences in pharmacokinetics (peak ranitidine concentrations, time to peak concentration, area under the serum-concentration time curve or elimination half-life) or pharmacodynamics (median intragastric pH or mean hydrogen-ion activity over the 23-h study interval). [25] Pounder *et al*, in a randomised trial in healthy volunteers, showed the exact timing of oral cimetidine administration in relation to meals was not critical. This difference between H_2RAs and PPIs, may offer an advantage to the H_2RAs as on-demand treatment for episodic postprandial dyspepsia or episodic postprandial heartburn (a patient who has already had a meal and developed postprandial symptoms, can only treat this episode with a medication that can be administered postprandial).[26]

Of note, most of our knowledge on the pharmacokinetics of PPIs and H_2RAs in relation to meals is derived from trials on healthy volunteers. However, we have no reason to expect that the results will be different in ambulatory patients.

H_2RA vs. PPI: Safety in pregnancy

An additional argument in favour of retaining H_2RAs in the WHO List of Essential Medicines, is their proven safety during pregnancy (interestingly there is an even higher need for acid suppression during pregnancy, because the prevalence of GERD is higher during pregnancy. According to the FDA labelling system for drugs in pregnancy, all H_2RAs (ranitidine, cimetidine, famotidine and nizatidine) are "relatively safe" in pregnancy and are classified as category B drugs. [27] Of the PPIs, lansoprazole, rabeprazole, pantoprazole and esomeprazole are also "relatively safe" in pregnancy and are also classified as category B drugs 33. However, there have been safety concerns about omeprazole in pregnancy (animal studies that showed that omeprazole in doses about 5.5 to 56 times the human dose was associated with dose-related embryo-lethality and fetal toxicity and postnatal developmental toxicity), therefore it is classified as category C drug. Epidemiological studies of pregnant women have revealed no evidence of adverse events of omeprazole on pregnancy or an increased risk of congenital malformations, but there these studies may have methodological limitations.[28]

H_2RA vs. PPI: Cost

H_2RAs cost less than PPIs in North America. Although PPIs are more effective than H_2RAs, some patients can be switched to H_2RAs are remain satisfied with their treatment. This is particularly important for low and middle income countries. However, it is important to note that internationally the range of the price for omeprazole (a PPI) is much higher than for ranitidine (an H_2RA). Therefore, it is possible that omeprazole may be purchased at a lower price than ranitidine in some countries.[29]

A double-blind, randomized trial published in 2005 compared two doses of esomeprazole (40 mg and 20 mg once daily) with standard-dose ranitidine for the healing of gastric ulcers in patients who continued to receive NSAIDs. Both doses of esomeprazole were superior to ranitidine.

Pipkin *et al* reported that, in GERD patients, oral ranitidine or famotidine had a faster onset of action compared to oral omeprazole or a lansoprazole: The H_2RAs achieved a significantly greater and more rapid rise in intragastric pH in the hour immediately after dosing and offered a faster relief of symptoms. This suggests that H_2RAs may be more effective than PPIs for on-demand treatment for episodic heartburn or episodic dyspepsia.[25]

After reviewing the available evidences, it has been concluded that:

1. Ranitidine (and other H2RAs) should not be deleted. PPIs are more effective than H2RAs in the management of gastro-oesophageal reflux disease (GERD) and or non-ulcer dyspepsia (NUD). However, H2RAs have advantages (some of which are particularly important for patients in developing countries): faster onset of action, no need to time administration before meals, lower cost, no fear of interaction with clopidogrel, probably safer in pregnancy. Furthermore, they can be used in patients who cannot tolerate PPIs because of side effects.[30]

2. There is a need for parenteral (intravenous) preparation of omeprazole (or another PPI) for patients experiencing acute bleeding from a peptic ulcer or patients who need potent acid suppression treatment but are unable to take oral PPIs.[31]

Misoprostol vs PPI / H_2RA

Two studies have compared omeprazole 20 mg once daily with standard-dose ranitidine (150 mg twice daily) and half-dose misoprostol (200 µg twice daily. These studies used a combined endpoint of endoscopically detected ulcer, multiple erosions and dyspepsia: omeprazole was superior to ranitidine and misoprostol.[32]

Graham *et al.* surveyed on two doses of lansoprazole (15 mg and 30 mg daily) with full-dose misoprostol (200 µg four times daily) in H. pylori-negative, chronic NSAID users who had a history of gastric ulcer. The results showed that full-dose misoprostol was more effective than either dose of lansoprazole for the prevention of gastric ulcer, on per-protocol analysis. There was no practical therapeutic advantage of misoprostol over lansoprazole, however, because of the high withdrawal rate in the misoprostol group.[33]

The fact that PPIs reduce, but do not eliminate, the risk of NSAID-induced ulcer complications suggests that acid-peptic injury is not the only mechanism involved in ulcer pathogenesis. Though it is rarely discussed, NSAIDs can produce ulcers in achlorhydric patients. It is uncertain whether PPIs remain effective in achlorhydric patients, and whether misoprostol has any advantage in these patients. Theoretically, it sounds attractive to combine half-dose misoprostol (which is well tolerated and provides 'physiologic prostaglandin replacement') and an antisecretory drug (e.g. omeprazole) because these two agents act via different mechanisms. Although this combination might provide inexpensive yet potentially effective ulcer prophylaxis for high-risk patients, it remains entirely unproven.[34]

As per the Current Clinical Guidelines: Current clinical guidelines published by the American College of Gastroenterology to prevent NSAID-induced ulcers stratify treatment strategy based on cardiovascular and gastrointestinal risk.

It is recommended that patients receive an NSAID plus either misoprostol or a PPI if they have low or moderate gastrointestinal risk. If the patient has high cardiovascular risk, naproxen is recommended as the NSAID. For patients with high gastrointestinal risk and low cardiovascular risk, a selective COX-2 inhibitor plus a PPI or misoprostol is recommended. Patients with both high gastrointestinal and cardiovascular risk should not receive any type of NSAID therapy. H2-receptor antagonists are much less effective compared to misoprostol or a PPI in preventing ulcers.[35]

Generally, NSAIDs or selective COX-2 inhibitors along with other analgesics such as acetaminophen are considered first line for the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.[36]

Other Key Facts

The NSAID is used to treat pain and inflammation while the anti-ulcer agent is used to prevent a common, yet severe adverse event associated with NSAIDs.

- Every combination's anti-ulcer component has a different mechanism of action.
- Diclofenac sodium/misoprostol is dosed three to four times a day based on indication; ibuprofen/famotidine is dosed three times; naproxen/esomeprazole magnesium is dosed twice daily.
- All agents in this class are tablets and share the same drug-interactions, warnings, precautions and black box warning associated with NSAIDs but differ based on their anti-ulcer component, particularly dosing.
- Only diclofenac sodium/misoprostol is available generically as a single-tablet combination.
- Naproxen/esomeprazole magnesium is approved to prevent gastric ulcers and is not indicated to prevent NSAID-associated duodenal ulcers.
- As single entity agents, all products are available generically, many of which are available over-the-counter.[37,38]

COX_2 & PPI / Misoprostol

The discovery of two COX isoforms, COX1 and COX2, and elucidation of their distinct biological functions, sparked an enormous drive to develop highly selective COX2 inhibitors as gastric-sparing NSAIDs. So far, five COX2 inhibitors have been evaluated in clinical trials:

celecoxib, rofecoxib, valdecoxib (and its prodrug paracoxib), etoricoxib, and lumiracoxib. Many endoscopic studies have shown that selective COX2 inhibitors cause fewer gastroduodenal ulcers than nonselective NSAIDs. Two large-scale, double-blind, randomized trials—the Vioxx® Gastrointestinal Outcomes Research Study (VIGOR)[39] and the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)[40] showed that rofecoxib and lumiracoxib cause significantly fewer clinical gastrointestinal events than nonselective NSAIDs. Unlike the VIGOR and TARGET trials, however, the Celecoxib Long-term Arthritis Safety Study (CLASS) failed to show a significant advantage of celecoxib over nonselective NSAIDs. Whether this failure was due to flaws in the study design remains controversial.[39]

Concomitant use of low-dose aspirin negates the gastrointestinal-sparing effect of COX2 inhibitors. Indeed, in the TARGET trial, there was no significant difference in the incidence of ulcer complications between the lumiracoxib group and the nonselective NSAID group in patients who received concomitant low-dose aspirin.−Another double-blind, randomized study showed that the rate of endoscopic detection of ulcers in patients who took both rofecoxib and low-dose aspirin was similar to that of patients who took ibuprofen.[40]

Preliminary data suggested that COX2 inhibitors cause less damage to the lower gastrointestinal tract than nonselective NSAIDs. Subgroup analysis from the VIGOR trial found that rofecoxib was associated with fewer lower gastrointestinal complications than naproxen. A study that used wireless video capsule endoscopy in healthy volunteers, showed that COX2 inhibitors caused less small-bowel mucosal injury than nonselective NSAIDs.[43] It is uncertain whether patients with arthritis who are at risk of lower gastrointestinal complications will benefit from COX2 inhibitors. [41]

There is evidence that COX2 inhibitors confer a comparable gastroprotective effect to that of a combination of nonselective NSAIDs and a PPI, in patients at high risk of ulcer complications. In a double-blind, randomized trial that compared diclofenac plus omeprazole with celecoxib in patients with a past history of ulcer bleeding, about 5% of patients in both groups had recurrent ulcer bleeding within 6 months. A follow-up endoscopic study found that the incidence of ulcer recurrence within 6 months was 19-26%. These findings indicate that although COX2 inhibitors provide a comparable gastroprotective effect to that of nonselective NSAIDs plus a PPI, neither treatment completely eliminates the risk of ulcers in very high risk patients. The combination of a COX2 inhibitor and a PPI or misoprostol probably offers the best gastrointestinal protection for very high risk patients, although this approach remains to be proven in prospective trials.[42]

AVAILABLE FORMULATIONS

S. No.	Combination	Reference
1.	Aspirin- Omeprazole	[44]
2.	Naproxen-Omeprazole	[45]
3.	Naproxen-Esomeprazole	[46]
4.	Ibuprofen/Famotidine	[47]
5.	Diclofenac sodium/Misoprostol	[47]
6.	Naproxen-pantoprazole	[48]
7.	Naproxen-Famotidine	[48]
8.	Aspirin- esomeprazole	[49]
9.	Celecoxib-esomeprazole	[50]
10.	Indomethacin-Omeprazole-Folic acid	[51]

CONCLUSION

Healing of NSAID related ulcers can be achieved while NSAIDs are continued by the use of H2-receptor antagonists in high doses are more effectively by proton pump inhibitors. Prevention of NSAID related gastrointestinal problems may be achieved by identifying and if possible reducing risk factors, the co-prescription of prostaglandin analogues or acid suppressive drugs (especially proton pump inhibitors), or by using the currently being developed and promising COX-2 specific inhibitors. The development of COX-2 specific inhibitors offers the hope of real progress in producing much safer and effective NSAIDs.

Misoprostol, when given in full doses (800 mcg / day) is very effective in preventing ulcers, and ulcer complications in patients taking NSAIDs. Unfortunately, its usefulness is limited by its GI side effects. When given in lower doses its side-effect profile is the same as that of PPIs, and it is equally effective.[33]

PPIs are more effective when administered before a meal. Most of our knowledge on the pharmacokinetics of PPIs and H_2RAs in relation to meals is derived from trials on healthy volunteers. However, we have no reason to expect that the results will be different in ambulatory patients.

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It has been concluded that, PPIs are superior then H2RA and Misoprostol on the following basis:

- High efficacy in ulcer treatment
- Long lasting effect of drug.
- It has most potent effect (low dose is required)
- Healing ulcer also in case of continuous NSAID therapy
- Does not causes any significant side effects (misoprostol causes diarrhoea).[14,43]

PPIs significantly reduce gastric and duodenal ulcer sand their complications in patients taking NSAIDs or COX-2 inhibitors. Although superior to placebo, high-dose H_2RAs can reduce the risk of NSAID-induced endoscopic peptic ulcers. -are significantly less effective than PPIs, however, there is no clinical outcome data to prove that this strategy prevents ulcer complications. [32]

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