Treatment and chemoprevention of NSAID-associated gastrointestinal complications

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Abstract: The use of non-steroidal anti-inflammatory drugs has become ubiquitous worldwide and remains a common source of gastrointestinal morbidity. Antisecretory medications, particularly proton pump inhibitors, are effective in the treatment and prevention of NSAID-related gastrointestinal complications, including peptic ulcer disease and non-ulcer dyspepsia. A careful assessment of patients' risk factors for developing NSAID-related gastrointestinal complications should be undertaken prior to initiation of any NSAIDs. Patients who are considered at risk for developing gastrointestinal complications should receive concurrent antisecretory medical therapy to minimize the risk for GI complications.

Keywords: NSAIDs, peptic ulcer disease, gastrointestinal prophylaxis

Introduction

Over one hundred million prescriptions for non-steroidal anti-inflammatory drugs (NSAIDs) were written in the US in 2000,[1] mostly for chronic pain syndromes and rheumatologic conditions. This likely represents only a fraction of NSAID use in the US due to the difficulty with tracking readily available over the counter (OTC) forms of these drugs, including aspirin and non-aspirin NSAIDs. Due to the aging population in the Western world the use of aspirin for the chemoprevention of cardiovascular, cerebrovascular, peripheral vascular disease and metabolic syndrome is likely to continue to increase. The recent widely publicized concerns regarding increased cardiovascular risks associated with cyclo-oxygenase-2 (COX-2) selective inhibitors has also contributed to increased use of non-selective NSAIDs.[2] The use of non-selective NSAIDs may further increase with recent interest in use of these drugs for the chemoprevention of colorectal cancer,[3] breast cancer,[4] and Alzheimer's disease.[5]

In spite of being among the most widely prescribed pharmaceuticals in the world, NSAIDs have long been recognized as a major cause of gastrointestinal morbidity. NSAID-associated gastrointestinal complications range from dyspepsia without endoscopic findings to severe complications such as ulcer-related perforation, obstruction, or hemorrhage. The use of chronic NSAIDs increases the risk of peptic ulcer disease complications by 3- to 5-fold. Overall, 15%–35% of all peptic ulcer complications are reportedly related to chronic NSAID use.[6] Moreover, major adverse gastrointestinal events attributed to NSAIDs are responsible for over 100,000 hospitalizations, US$2 billion in healthcare costs, and 17,000 deaths in the US each year.[7] Despite improvements in the available medications to aid in healing and treatment of NSAID-associated complications, the number of hospitalizations and deaths has remained unchanged in the US in the last decade. While clinically significant complications such as perforation, obstruction, or hemorrhage are relatively uncommon (1%–2% of all NSAID users, overall incidence of 2%–4% per year),[8] gastrointestinal symptoms including nausea, heartburn, dyspepsia, and abdominal pain are extremely common and may

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occur in up to 40% patients taking chronic NSAIDs.[9,10] Despite being clinically effective in treating the underlying disease, gastrointestinal symptoms may negatively impact quality of life enough to warrant either dose reduction or discontinuation of the drug.[11] Certain groups of persons taking NSAIDs are at increased risk for developing NSAID-related complications, including patients with prior history of peptic ulcer disease, the elderly, patients taking high dose NSAIDs, and patients taking concurrent anticoagulation or corticosteroids.[12,13] Therapeutic strategies to reduce NSAID-associated gastrointestinal complications have focused on the treatment of acute events such as peptic ulcer disease and the prevention of future events in patients who continue taking chronic NSAIDs. Historically, the most widely employed prevention strategies involved either cyclo-oxygenase 2 (COX-2) selective inhibitors or co-administration of a nonselective NSAID with a proton pump inhibitor. This paper will review medical therapy for primary treatment and the indications for primary and secondary prophylaxis for NSAID-associated gastrointestinal complications including peptic ulcer disease and non-ulcer dyspepsia.

Pathogenesis of NSAID-associated peptic ulcer disease

Non-steroidal anti-inflammatory medicines and *Helicobacter pylori* are known to independently and significantly increase the risk for gastroduodenal ulcer and ulcer bleeding. This has important diagnostic and treatment implications as both ulcerogenic factors are highly prevalent. Moreover, the relationship between *H. pylori* infection and NSAID use has important diagnostic and treatment implications, particularly in patients who take NSAIDs and have concurrent *H. pylori* infection. While it is generally thought that *H. pylori* infection and NSAIDs induce mucosal damage by different mechanisms, there is ongoing debate whether their coincidence is independent, additive, synergistic, or antagonistic.[14] Whether or not eradication of *H. pylori* modifies the ulcer risk in patients who require chronic NSAIDs remains a topic of debate.

Mucosal injury caused by NSAIDs likely occurs by several different mechanisms and can be broadly divided into topical and systemic effects. Most NSAIDs, including aspirin, are carboxylic acid derivatives and consequently are not ionized in the acidic pH found in the stomach. The nonionized drug is readily absorbed across the gastric mucosa into the pH-neutral mucosa where it is ionized and temporarily trapped within the epithelial cells. The high intracellular concentration of drug may induce cellular injury and ultimately cause damage to the gastrointestinal mucosa.

The systemic effects exhibited by the post-absorptive inhibition of gastrointestinal cyclooxygenase (COX) activity likely plays a more central role in the pathogenesis of NSAID-induced ulcers. Indeed, peptic ulcer disease has been demonstrated in humans following the intravenous and intramuscular administration of NSAIDs, which suggests a systemic mechanism of action.[15,16] Cyclooxygenase, which is present in at least two isoforms in humans, is the principal enzyme involved in the biochemical conversion of membrane phospholipid, arachidonic acid, into prostaglandins. Various prostaglandins may either prevent or potentiate the inflammatory response. Like most tissue, healthy gastric and duodenal mucosae constitutively express COX-1, which produces prostaglandins that act locally in the stomach and duodenum to help protect against mucosal injury. In contrast, the expression of COX-2 occurs largely in response to inflammatory mediators and generates various prostaglandin effectors that are responsible for attenuating the inflammatory response.

NSAIDs exert their effects by interfering with prostaglandin production through the direct inhibition of cyclooxygenase activity. From a gastrointestinal standpoint, the ideal NSAID would inhibit the inducible COX-2 isoform, thereby reducing inflammation, without acting on COX-1 and its constitutively expressed cytoprotective effectors. Most NSAIDs, including aspirin and ibuprofen inhibit COX-1 and COX-2 equally. However, some NSAIDs, such as celecoxib, selectively inhibit COX-2 and exhibit less suppression on the locally protective gastric prostaglandins. The inhibition of COX-1 and the loss of the protective gastrointestinal prostaglandins may cause a local ischemic injury by reduction in mucosal blood flow at the submucosal and mesenteric levels.[17,18] While associated with less gastrointestinal toxicity, selective COX-2 inhibitors are still associated with some risk for gastrointestinal toxicity particularly at higher doses and in high risk patients.[19,20] Recently publicized concerns regarding the increased cardiovascular and thromboembolic risk in patients taking selective COX-2 inhibitors and high doses of some nonselective NSAIDs has led to a global re-evaluation of the use of these drugs in clinical practice.[21] Novel drugs with improved safety profile throughout their therapeutic range which selectively inhibit COX-2 are desirable and will likely reduce adverse gastrointestinal events.

Medical therapy for NSAID-associated peptic ulcer disease

The treatment of peptic ulcer disease in patients who test negative for *H. pylori* relies on prompt discontinuance of the

potential causative agent, such as NSAIDs, and the initiation of medical therapy to promote ulcer healing. Options for medical treatment include cytoprotective agents including sucralafate and the prostaglandin analogue misoprostol, the latter aims to restore the prostaglandins which become depleted by COX-1 inhibition. Acid-suppressive agents including histamine-2 antagonists (H_2RAs) and proton pump inhibitors (PPIs) have also been employed as medical therapy.

Primary treatment of NSAID-associated peptic ulcer disease

Whenever possible, the primary treatment for NSAID-associated peptic ulcer disease should include discontinuing potential causative agents. In some instances this may not be possible due to concerns that the underlying chronic disease being treated may worsen if therapy is stopped. This commonly occurs in patients with vascular diseases, especially coronary artery disease, which may pose high risk if antiplatelet therapy such as aspirin is discontinued.

Numerous studies have evaluated endoscopic ulcer healing rates in the context of continued NSAID use. It is important to recognize that studies using endoscopic healing rates as a primary end point may not be clinically significant as most ulcers endoscopic ulcers do not cause clinically significant complications such as perforation, obstruction, or hemorrhage. The use of H_2RAs has been widely studied in the treatment of acid-related disorders. Endoscopic healing rates of gastric and duodenal ulcerations have been reported between 50%–84% after 8 weeks of treatment, with higher healing rates generally observed with treatment of duodenal ulcers.[22] Lancaster-Smith, et al performed a multi-center endoscopic surveillance study on 190 patients with confirmed gastric or duodenal ulcerations attributed to NSAIDs.[23] All patients received ranitidine 150 mg twice daily and were randomized to either continue or discontinue NSAID treatment. The 8-week endoscopic healing rates were 95% and 100% for gastric and duodenal ulcers, respectively, in patients who received H_2RA and discontinued NSAIDs. The authors noted that healing rates were much lower (63% and 84% for gastric ulcer and duodenal healing, respectively) in patients treated with H_2RA who remained on NSAIDs throughout the treatment period.[23] Manniche et al performed an open-label study comparing ranitidine 150 mg twice daily with sucralafate 1 g 4 times daily in patients with NSAID-associated peptic ulcer disease.[24] Half of the patients in each treatment group were allowed to continue NSAID therapy while the other half was given an alternative non-NSAID analgesic medication. The overall healing rates were comparable between the two groups (81% for ranitidine, and 84% for sucralafate) at 9 weeks. Healing rates were improved in patients who discontinued NSAIDs during primary treatment, 92% versus 85%, respectively.[24] There have been no randomized trials to date comparing misoprostol to H_2RAs in the primary treatment of NSAID-associated peptic ulcer disease.

The extent of gastroduodenal mucosal damage caused by NSAIDs is highly dependent on the intraluminal gastric pH. Low intragastric pH enhances the diffusion of NSAIDs into the gastric mucosa and may facilitate mucosal injury.[25] Moreover, H_2RAs have been associated with variations in 24-hour acid suppression.[26] The profound and sustained acid suppressive effects exhibited by proton pump inhibitors have revolutionized the treatment of acid-related gastrointestinal diseases. Amongst patients continuing chronic NSAIDs and taking proton pump inhibitors, once-daily esomeprazole (74.2%) has been shown to have a greater mean percentage time with gastric pH $>$ 4 during 24-hour pH monitoring compared to once-daily lansoprazole (66.5%) and pantoprazole (60.8%).[27]

Multiple clinical trials have evaluated ulcer healing rates using proton pump inhibitors in chronic NSAID users. The Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment (ASTRONAUT) trial (Yeomans, et al) studied 541 patients who required continuous NSAIDs and had demonstrable peptic ulcer disease.[28] Patients were randomized to receive either 20 mg or 40 mg omeprazole daily, or 150 mg ranitidine twice daily and were followed for endoscopic healing. At eight weeks, treatment was successful in 80% of the patients in the 20 mg omeprazole group, 79% of the patients in the 40 mg omeprazole group, and 63% of the patients in the ranitidine group. Following endoscopic resolution, significantly more patients remained in remission at 6-month follow-up in the group receiving omeprazole (72%) than the ranitidine group (59%). The authors concluded that omeprazole is superior to ranitidine in healing and preventing recurrence of NSAID-associated ulcers in patients who use chronic NSAIDs.[28]

In the multi-national, double-blind Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management (OMNIUM) study, Hawkey, et al randomly assigned 935 patients with established NSAID-associated ulcers to receive either 20 mg omeprazole daily, 40 mg omeprazole daily, or 200 μg misoprostol four times daily while remaining

on NSAID therapy.[29] Endoscopic healing rates were higher in the omeprazole groups (76% in group receiving 20 mg, and 75% in group receiving 40 mg) compared with the misoprostol group (71%). Once endoscopic healing was achieved, 732 patients were treated for 6 months with maintenance therapy, either 20 mg omeprazole, 200 μg misoprostol twice daily, or placebo. Significantly more patients remained in remission with omeprazole (61%) than with misoprostol (48%) and with either drug than with placebo (27%) during the 6 month maintenance treatment period.[29] It is worth noting that maintenance treatment dose of misoprostol was lower than approved doses. The authors concluded that both doses of omeprazole were similar to misoprostol in the treatment of NSAID-associated peptic ulcer disease. In addition, maintenance therapy with omeprazole was associated with a lower rate of relapse than misoprostol and was better tolerated than misoprostol due to treatment associated diarrhea and abdominal pain. Another large, prospective, double-blind, multi-center study evaluated 537 patients with endoscopic-proven gastric ulcers attributed to NSAIDs. This study addressed some of the limitations in the ASTRONAUT and OMNIUM trials by ensuring that all patients tested negative for Helicobacter pylori at the time of enrollment. Prior studies have shown that gastoduodenal outcome in chronic NSAID users who are infected with *H. pylori* is different than patients without infection.[30,31] In addition, the misoprostol treatment arm used approved treatment doses of the drug during the entire treatment period. Graham, et al randomized patients to treatment with either placebo, 200 μg misoprostol four times daily, or lansoprazole (15 mg or 30 mg) daily and were allowed to continue NSAIDs during the six month treatment period.[32] Patients were followed with serial endoscopic evaluations at 4, 8, and 12 weeks during treatment. The 12-week gastric ulcer-free rates were significantly higher in the groups treated with lansoprazole (80% and 82%, in 15 mg and 30 mg lansoprazole, respectively) and misoprostol (93%) compared to placebo (51%). The authors also noted that while effective in prevention of gastric ulcer relapse, the misoprostol treatment group had a significantly higher rate of treatment-related side effects and early withdrawal compared to the lansoprazole group.[32] Goldstein et al performed a similar study comparing 20 mg or 40 mg esomeprazole and ranitidine 150 mg twice daily in 406 patients receiving NSAIDs with endoscopically confirmed peptic ulcer disease.[33] The 8-week healing rates with esomeprazole 40 mg and 20 mg were 91.5% and 88.4%, respectively, and were significantly higher than the 74.2% rate with ranitidine.[33]

Secondary prophylaxis of NSAID-induced peptic ulcer disease

Once resolution of NSAID-associated peptic ulcer disease has been demonstrated, a careful assessment of risks and benefits of continued NSAID therapy should be undertaken before reinitiation or continued NSAID therapy. A number of risk factors have been identified that may be helpful in predicting an increased risk for NSAID-related complications (Table 1). Importantly, a history of complicated peptic ulcer disease and use of multiple NSAIDs are the major risk factors for recurrent complications with odds ratios of 13.5 and 9, respectively. Prevention strategies are recommended in patients with significant risk factors who are unable to discontinue NSAIDs or who have high risk medical comorbidities that favor continued NSAID therapy, particularly in those patients with cardiovascular or cerebrovascular disease who require continued aspirin therapy.

Two large similarly designed randomized, double-blind, placebo-controlled trials assessed ulcer prevention in high-risk patients who were either >60 years of age and/or had documented peptic ulcer disease within five years prior to enrollment.[34] All patients were on stable doses of NSAIDs (including COX-2 inhibitors) for at least 4 weeks prior to the study, tested negative for *H. pylori*, and had no endoscopic findings to suggest peptic ulcer disease at time of enrollment. The Verification of Esomeprazole for NSAID Ulcers and Symptoms (VENUS) study performed in 110 centers throughout the United States and the international equivalent, Prevention of Latent Ulceration Treatment Options (PLUTO) study, enrolled a total of 844 and 585 patients, respectively, all of whom were randomized to receive either 20 mg or 40 mg esomeprazole

Table 1 Risk factors for development of peptic ulcer disease related to nonsteroidal anti-inflammatory drugs[52,53,54,55,56,57]

Risk factor	Risk equivalent
Prior history of complicated PUD	OR 13.5
Multiple (≥2) NSAIDs	OR 9
Co-administration of NSAID + aspirin	SIR 5.6
High dose NSAIDs	OR 7
Co-administration NSAID + anticoagulant	OR 6.4
Prior history of uncomplicated PUD	OR 6.1
Age > 70	OR 5.6
Co-administration of NSAID + corticosteroids	OR 2.2

Abbreviations: PUD, peptic ulcer disease; OR, odds ratio; SIR, standardized incidence ratio.

or placebo daily for 6 months. Patients were assessed for development of upper GI symptoms and underwent physical examination and upper endoscopy at baseline and after 1, 3, and 6 months of treatment. The estimated proportion of patients developing peptic ulcer disease over the 6-month study period in the VENUS study was 20.4% on placebo, 5.3% on 20 mg esomeprazole, and 4.7% on 40 mg esomeprazole daily. The estimated proportions were similar in the PLUTO study 12.3% on placebo, 5.2% on 20 mg esomeprazole, and 4.4% on 40 mg esomeprazole daily. A similar risk reduction was observed in patients taking esomeprazole regardless of whether patients were taking non-selective NSAIDs or COX-2 inhibitors. The authors concluded that for high risk patients, esomeprazole was well-tolerated and effective in preventing peptic ulcer disease in patients taking chronic NSAIDs.[34]

Combination treatment with a proton pump inhibitor and a selective COX-2 inhibitor has been suggested for optimal gastrointestinal protection in the highest risk patients, particularly those who have had complicated peptic ulcer disease. Chan, et al evaluated 273 patients with documented NSAID-associated peptic ulcer disease. After endoscopic healing was confirmed and *H. pylori* (if present) was eradicated, all patients were started on celecoxib 200 mg twice daily and randomized to either esomeprazole 20 mg twice daily or placebo for 12 months. The primary end point of recurrent ulcer bleeding was 0% in the esomeprazole group and 8.9% in the placebo group. The authors concluded that esomeprazole plus celecoxib was superior to celecoxib alone for the prevention of recurrent ulcer bleeding in patients with history of NSAID-induced ulcer bleeding.[35]

Primary prophylaxis of NSAID-induced peptic ulcer disease

It is widely accepted that antisecretory medications, particularly proton pump inhibitors, are effective in the primary treatment and prevention of recurrent NSAID-associated peptic ulcer disease. Primary prophylaxis for prevention of gastrointestinal complications in chronic NSAID users has been more controversial

Raskin et al compared misoprostol and ranitidine in 538 chronic NSAID users with normal baseline upper endoscopy. Misoprostol was shown to be significantly more effective in the prevention of NSAID-induced gastric ulcers compared to the H2RA ranitidine (0.56% versus 5.67%) in the 8-week trial period. Prevention rates were similar between misoprostol (1.10%) and ranitidine (1.08%) for duodenal ulcers, but ranitidine was better tolerated.[36] The multinational Omeprazole versus Placebo as Prophylaxis against ULcers or Erosions from NSAID Treatment (OPPULENT) study conducted by Cullen, et al evaluated the primary prevention of peptic ulcer disease using once daily omeprazole (20 mg) versus placebo in 169 patients taking chronic NSAIDs with no demonstrable peptic ulcer disease. A total of 16.5% patients treated with placebo developed gastric or duodenal ulcerations compared to only 3.6% patients treated with omeprazole during the six month treatment period.[37] Regula et al performed another primary prevention study evaluating the use of daily pantoprazole (20 mg or 40 mg), omeprazole (20 mg) in 595 chronic NSAID users with no evidence of peptic ulcer disease on baseline upper endoscopy. After 6 months, the probabilities to remain in remission in the pantoprazole groups were 90% and 93% (20 mg and 40 mg, respectively) and 89% in the omeprazole group. The authors concluded that both doses of pantoprazole and omeprazole provide equivalent, effective, and well-tolerated primary prophylaxis against the endoscopic development of peptic ulcer disease in chronic NSAID users.[38]

While most COX-2 inhibitors are no longer widely available due to safety concerns, these drugs provided an alternative strategy in primary and secondary prophylaxis of gastrointestinal complications related to chronic NSAIDs. Several large outcomes studies have demonstrated significantly fewer clinically important upper gastrointestinal events in patients treated with selective COX-2 inhibitors compared to non-selective NSAIDs.[9,39,40] In the Vioxx GI Outcomes Research (VIGOR) study, patients with rheumatoid arthritis were assigned to receive full treatment doses of either naproxen or rofecoxib and followed for gastrointestinal complications such as hemorrhage, perforation, or obstruction. Overall, the rofecoxib group showed a 40% relative risk reduction in GI complications compared to the naproxen group. By contrast, the Celecoxib Long-term Arthritis Safety Study (CLASS), which compared treatment doses of celecoxib and diclofenac, demonstrated similar rates of ulcers and ulcer complications between the two groups. A post hoc analysis suggested that lack of difference was due to the relatively large number of patients in the celecoxib group allowed to take concomitant low-dose aspirin for primary and secondary prevention of cardiovascular and cerebrovascular disease. Whether aspirin abrogates the potentially protective benefits of selective COX-2 inhibitors remains controversial and patients receiving both aspirin and a selective COX-2 inhibitor may

require prophylactic antiulcer therapy if they are at risk for gastroduodenal toxicity.

Secondary prophylaxis of NSAID-induced peptic ulcer disease using other antiplatelet agents

Aspirin has a known dose-related risk of gastrointestinal adverse events, particularly in elderly patients.[41] New antiplatelet drugs, such as the adenosine diphosphate receptor inhibitor clopidogrel, have been proposed as an alternative therapeutic medication in the prevention and treatment of vascular diseases. The 2000 American College of Cardiology-American Heart Association Guidelines recommended the use of clopidogrel for hospitalized patients with coronary syndromes who are unable to take aspirin because of major gastrointestinal intolerance.[42] This has prompted investigators to evaluate the risk of recurrent ulcer bleeding using other antiplatelet medications. Chan et al randomized 320 patients with a history of peptic ulcer disease attributed to aspirin to receive 75 mg clopidogrel daily with placebo twice daily or 80 mg aspirin daily with 20 mg esomeprazole twice daily.[43] All patients tested negative for *H. pylori* and had endoscopically confirmed ulcer healing prior to enrollment. During the 12 month treatment period, a total of 13 patients in the clopidogrel group developed a recurrent ulcer bleed compared to 1 patient in the aspirin plus esomeprazole group. The cumulative 12-month incidence was 8.6% for clopidogrel versus 0.7% for aspirin with esomeprazole. The authors concluded that the risk of gastrointestinal bleeding in the aspirin plus esomeprazole group was significantly lower than the clopidogrel group and therefore superior in the prevention of recurrent ulcer bleeding.[43] While the mechanism remains unknown, this study provides supportive evidence that clopidogrel poses a significant risk of peptic ulcer disease and does not support the proposed 2000 ACC/AHA guidelines for use of clopidogrel in patients with previous gastrointestinal intolerance.

The withdrawal of some COX-2 inhibtors (rofecoxib and valdecoxib) from global markets has led to new prevention strategies against upper GI complications. The potential protective effects of nitrovasodilators are of particular interest considering that concurrent use of aspirin and nitrates is common in patients with cardiovascular disease. Nitrates and nitric-oxide releasing drugs are believed to exert their protective effects by maintaining mucosal blood flow at the level of the gastroduodenal microcirculation, thereby counteracting one of the principal deleterious effects of COX-1 inhibition. Indeed, both experimental and epidemiological studies have consistently demonstrated a reduced risk of gastroduodenal damage and ulcer bleeding with concomitant use of nitrates or nitric-oxide releasing agents and NSAIDs.[44,45,46] A recent case-control study by Lanas, et al analyzed the concomitant use of anti-secretory medications and nitrates on the risk of ulcer bleeding in 2777 consecutive patients with upper gastrointestinal hemorrhage compared to 5532 controls.[47] The use of NSAIDs (including aspirin at any dose) was associated with an increased relative risk (RR) of upper gastrointestinal hemorrhage (RR 5.6, 95% CI 5.0–6.3). Consistent with previous data, the concomitant use of proton pump inhibitors, H2RAs, and nitrates was associated with an 82%, 61%, and 49% reduction in risk of upper gastrointestinal hemorrhage, respectively. When patients were stratified according to the use of other antiplatelet agents (eg, clopidogrel) or anticoagulants (eg, dicumarinics), the RR of upper gastrointestinal hemorrhage was 3.2 (95% CI 2.2–4.4 and 95% CI 2.5–4.0, respectively), which is comparable to risk associated with low dose aspirin. Interestingly, only concomitant use of proton pump inhibitors and not H2RAs or nitrates was associated with risk reduction in patients taking non-NSAID antiplatelet medications (81%) and none of these preventive agents were associated with a statistically significant risk reduction among anticoagulant users. The authors concluded that based on these observational data, there was a clear benefit from co-administration of antisecretory drugs and nitrates in prevention of upper GI peptic ulcer bleeding associated with NSAIDs, including aspirin. Moreover, these data suggest that profound acid suppression as exhibited by proton pump inhibitors may prevent ulcer bleeding in patients treated with non-NSAID antiplatelet drugs.

Treatment of NSAID-associated gastrointestinal symptoms

Another important aspect in the treatment of NSAID-associated gastrointestinal complications relates to the treatment of upper GI symptoms associated with chronic NSAID use. Indeed, as many as 40% patients treated with chronic NSAIDs may experience upper gastrointestinal symptoms such as dyspepsia, abdominal pain, and heartburn.[10] It is important to realize, however, studies have demonstrated little correlation between gastrointestinal symptoms and endoscopic findings in patients taking chronic NSAIDs. For example, in one study 46% of asymptomatic patients taking low dose aspirin (100–325 mg daily) had ulcerations found in the stomach or duodenum at time of endoscopy.[48] In another study, the first sign of a peptic ulcer disease was a life-threatening complication in 58% of patients using chronic NSAIDs.[49] Nonetheless, many patients require NSAIDs to control their primary underlying chronic

disease and cannot tolerate dose reduction, interruption, or discontinuation of the drug. Multiple studies have been conducted to address whether antisecretory agents are effective in controlling gastrointestinal symptoms related to NSAIDs despite the absence of endoscopic findings. Hawkey et al performed a large multicenter trial to evaluate the clinical response in upper gastrointestinal symptoms attributed to NSAIDs (including COX-2 inhibitors) treated with esomeprazole.[50] A total of 608 and 556 chronic NSAID users, respectively, were randomized to treatment in the two identical Nexium Anti-Inflammatory Symptom Amelioration (NASA1) and Symptoms Prevention by Acid Control with Esomeprazole (SPACE1) protocols. All patients were endoscopically free of gastroduodenal ulcerations, erosive esophagitis, and tested negative for *H. pylori* at enrollment. Patients were continued on previously stable doses of NSAIDs and were randomized to treatment with either once daily esomeprazole (20 mg or 40 mg) or placebo. A standardized gastrointestinal symptom rating scale (GSRS) was used to measure patient-reported upper GI symptoms including reflux, abdominal pain, and indigestion on a 7-point severity scale at baseline and after 4 weeks of medical therapy. The primary endpoint was the patients' mean change in the upper GI symptom score between baseline and the end of the study. Patients in both the NASA1 and SPACE1 trials treated with both doses of esomeprazole had highly significantly improvement in symptoms based on mean change in GSRS (2.30 and 2.17 on 20 mg esomeprazole for NASA1 and SPACE1, respectively; 2.03 and 2.12 on 40 mg esomeprazole for NASA1 and SPACE1, respectively) compared to placebo (1.64 and 1.56 for NASA1 and SPACE1, respectively). The improvement in upper GI symptoms occurred in patients regardless of whether they were taking non-selective NSAIDs or COX-2 inhibitors. The authors acknowledged a large placebo effect with regards to GI symptom scores and overall treatment effect, which has been previously demonstrated in numerous other studies of GI symptoms. Subjective clinical improvement may reflect patient reassurance that more serious diseases have been excluded by close serial observation in a clinical trial environment. The authors concluded that esomeprazole improves upper gastrointestinal symptoms associated with chronic NSAID use, including selective COX-2 inhibitors.[50]

Conclusion

High healing rates of peptic ulcers related to chronic NSAID use are achieved with medical therapy, particularly if the causative agent can be discontinued. The American Gastroenterological Association (AGA) recently released a consensus statement regarding the use of NSAIDs following a panel discussion of physicians in gastroenterology, rheumatology, cardiology, and internal medicine. The panel emphasized a careful review of treatment indications and risk factors, taking into careful consideration risks for both gastrointestinal and cardiovascular complications.[51] Recommendations are summarized in Figure 1. If the causative agent cannot be discontinued, a

A. Primary treatment of endoscopically confirmed peptic ulcer disease
    1. Perform careful risk assessment including gastrointestinal and cardiovascular risks
    2. Discontinue NSAID/aspirin, if possible
    3. Eradicate *Helicobacter pylori* infection, if present
    4. Antisecretory therapy to promote ulcer healing (PPIs are superior to H_2RAs)

B. Prevention of NSAID-associated ulcer recurrence (ie, primary or secondary prophylaxis)
    1. Perform careful risk assessment including gastrointestinal and cardiovascular risks
    2. Eradicate *Helicobacter pylori* infection, if present
    3. Consider substitution for a non-NSAID analgesic
    4. Consider dose reduction of NSAID
    5. Add PPI co-therapy if NSAID is continued (misoprostol may be considered as second line agent, if tolerated)
    6. Consider switching to COX-2 inhibitor after careful assessment of cardiovascular risk factors

Figure 1 Management strategies for NSAID-associated gastrointestinal complications.

reduced dose or switch to a more COX-2 selective NSAID in conjunction with co-administration of PPIs to promote ulcer healing should be considered. Misoprostol has been shown to be effective in reducing the risk of gastric ulcers in patients at high risk for complications from NSAIDs including the elderly and patients with previous history of peptic ulcer disease. It has not been demonstrated to reduce the risk of duodenal ulcerations nor reduction in symptoms related to chronic NSAIDs. Moreover, misoprostol has a high frequency of intolerance due to gastrointestinal side effects. H2-receptor antagonist therapy is inadequate for patients receiving NSAIDs with risk factors for GI complications; moreover, they have been supplanted by the highly efficacious and well tolerated proton pump inhibitors. Lansoprazole has been shown to be effective in the primary treatment and secondary prophylaxis of NSAID-associated peptic ulcer disease, including maintenance therapy following resolution of duodenal ulcers. Esomeprazole is the only proton pump inhibitor shown to be effective in both primary and secondary prophylaxis of NSAID-associated peptic ulcer disease. Esomeprazole has also been shown to be highly effective in reducing non-ulcer related symptoms associated with chronic NSAID use and may help reduce risk of bleeding from non-NSAID antiplatelet drugs. The aforementioned clinical studies provide supportive evidence for the use of antisecretory medicine, especially PPIs, in the primary treatment of NSAID-associated peptic ulcer disease. Peptic ulcer disease and related complications may be prevented in chronic NSAID users with primary prophylactic use of adequate doses of misoprostol and anti-secretory medicines, especially PPIs. Aggressive prevention strategies should be undertaken in high-risk patients especially those with a history of peptic ulcer disease to prevent against recurrent peptic ulcer disease and its associated complications.

Disclosures

The authors have no conflicts of interest to disclose.

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