NSAIDs (including aspirin): Primary prevention of gastroduodenal toxicity

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, cause considerable morbidity and mortality related to gastric and duodenal mucosal injury [1]. Thus, prevention of NSAID-induced GI toxicity is an important clinical issue.

The prostaglandin E analog misoprostol, H2 receptor antagonists, and proton pump inhibitors (PPIs) have been evaluated as prophylactic therapies for patients taking NSAIDs. In addition, the selective COX-2 inhibitors (coxibs) is another strategy for the reduction of NSAID-related gastroduodenal toxicity. However, concerns about cardiovascular toxicity has limited development and marketing of coxibs. (See "Overview of COX-2 selective NSAIDs" and "NSAIDs: Adverse cardiovascular effects".)

Strategies for the primary prevention of gastroduodenal toxicity due to NSAIDs and low-dose aspirin will be reviewed here. Emphasis will be placed upon studies that used clinically relevant end points (symptomatic ulcers and complicated ulcers, including bleeding, perforating, and obstructing ulcers). Studies using endoscopic detection of ulcers as the end point will be cited only when data on more meaningful clinical end points are sparse or lacking. The pathogenesis, treatment, and secondary prevention of NSAID-induced gastroduodenal injury are discussed separately. (See "NSAIDs (including aspirin): Pathogenesis and risk factors for gastroduodenal toxicity" and "NSAIDs (including aspirin): Treatment and secondary prevention of

gastroduodenal toxicity" and "NSAIDs (including aspirin): Secondary prevention of gastroduodenal toxicity".)

RISK FACTORS

Studies have evaluated risk factors for gastroduodenal toxicity from nonsteroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin and assessment of these factors is recommended for identifying patients who should be considered for primary prophylaxis if it is felt that an NSAID or low-dose aspirin must be given [2-5]. (See "NSAIDs (including aspirin): Pathogenesis and risk factors for gastroduodenal toxicity".)

One prospective study of 34,701 osteoarthritis and rheumatoid arthritis patients ages 50 and above randomized to either a coxib or diclofenac use found the following factors to be significant predictors for gastrointestinal (GI) toxicity including bleeding, perforation, obstruction, or uncomplicated ulcer: age >64, a history of prior adverse GI events, or concurrent use of low-dose aspirin [6].

In the ASPREE primary prevention of cardiovascular disease trial of 19,114 persons aged 70 years or above, low-dose aspirin therapy increased upper GI bleeding (hazard ratio [HR] 1.87; 95% CI 1.32-2.66), without leading to significant cardiovascular benefit [5].

According to 2008 American College of Cardiology Foundation/American College of Gastroenterology (ACG)/American Heart Association guidelines, patients with the following factors are considered to be at high risk for GI toxicity from NSAIDs [4]:

- History of ulcer disease or ulcer complication
- On dual antiplatelet therapy
- On anticoagulant therapy
- Have two or three of the following:
    - Age ≥60 years
    - Glucocorticoid use
    - Dyspepsia or gastroesophageal reflux disease symptoms

In separate guidelines from the ACG in 2009, patients taking NSAIDs were classified as being at high, moderate, or low risk for gastroduodenal toxicity [7]:

- High risk was defined as a history of a complicated ulcer or ≥3 risk factors
- Moderate risk was defined as the presence of one or two risk factors
- Low risk was defined as none of the four risk factors

The four risk factors are:

- History of an uncomplicated ulcer
- Age >65 years
- High-dose NSAID therapy
- Concurrent use of aspirin (including low dose), glucocorticoids, or anticoagulants

Use of selective serotonin reuptake inhibitors (SSRIs) has also been associated with an increased risk of GI bleeding [8,9]. A meta-analysis of observational studies showed an odds ratio of 2.36 (1.44-3.85) for SSRI associated upper GI hemorrhage. The odds ratio increased to 6.33 (3.40-11.8) for concurrent SSRI and NSAID use [8]. (See "NSAIDs (including aspirin): Pathogenesis and risk factors for gastroduodenal toxicity".)

A large case series analysis involving over 100,000 patients with upper GI bleeding demonstrated that monotherapy with SSRIs, glucocorticoids, aldosterone antagonists, nitrates, and calcium channel blockers was associated with an increased risk of bleeding [9]. Furthermore, glucocorticoids and aldosterone antagonists added to the risk of bleeding when used together with nonselective NSAIDs [9].

NONSELECTIVE NSAIDs

In a 2013 meta-analysis that utilized data from over 300,000 participants in over 750 trials, all NSAID regimens examined increased upper gastrointestinal complications including upper gastrointestinal perforation, obstruction, or bleeding (adjusted rate ratio [ARR] for diclofenac 1.89, 95% CI 1.2-3.1; ibuprofen 3.97, 95% CI 2.2-7.1; and naproxen 4.2, 95% CI 2.7-6.6) when compared to placebo [10].

In another meta-analysis of controlled trials involving some of the most commonly prescribed NSAIDs, the following conclusions were reached [11]:

- The risk of gastrointestinal complications was highest with indomethacin (relative risk [RR] 2.25), followed by naproxen (RR 1.83), diclofenac (RR 1.73), piroxicam (RR 1.66), tenoxicam (RR 1.43), ibuprofen (RR 1.19), and meloxicam (RR 1.24).

- The risk was related to the duration of treatment. The average duration of treatment before observing a significant risk of GI effects was 84 days. However, an increased risk was apparent as early as seven days with indomethacin.

Similar conclusions were reached in an earlier meta-analysis, which ranked the risk of various NSAIDs relative to ibuprofen, which at the time was considered to have the lowest risk [12]. A

ranking of increasing risk was found in the following order: ibuprofen, fenoprofen, aspirin, diclofenac, sulindac, diflunisal, naproxen, indomethacin, piroxicam, ketoprofen, and azapropazone.

A cohort study conducted in United States veterans suggests that the NSAID etodolac caused significantly fewer clinically significant upper gastrointestinal events than naproxen, an effect that was eliminated by concurrent treatment with low-dose aspirin [13].

Ulcer risk also increased with higher doses of the NSAIDs in the aforementioned meta-analysis [11]. The following relative risks were observed in a subset of studies that had described GI toxicity relative to the dose of the NSAID:

- Low-dose ibuprofen (RR 1.6, 95% CI 0.8-3.2)
- High-dose ibuprofen (RR 4.2, 95% CI 1.8-9.8)
- Low-dose naproxen (RR 3.7, 95% CI 1.7-7.7)
- High-dose naproxen (RR 6.0, 95% CI 3.0-12.2)
- Low-dose indomethacin (RR 3.0, 95% CI 2.2-4.2)
- High-dose indomethacin (RR 7.0, 95% CI 4.4-11.2)

While the dosing cutoffs defining "high" versus "low" were somewhat arbitrary and varied across studies, they nevertheless support the observation that the risk associated with NSAIDs is related not only to the duration of therapy but also to the dose of treatment. (See "Aspirin in the primary prevention of cardiovascular disease and cancer", section on 'Bleeding'.)

Ketorolac, which was not included in the above meta-analyses, is also associated with a high risk of GI toxicity, particularly when used in higher doses, in older patients, and for more than five days [14]. One study found that ketorolac was 5.5 times more likely to cause GI toxicity than other NSAIDs [15]. Because of the risks associated with ketorolac (both gastrointestinal and renal), its use should be restricted to short-term pain treatment [16,17]. (See "Nonselective NSAIDs: Overview of adverse effects".)

ENTERIC-COATED AND BUFFERED ASPIRIN

It has been proposed that a way to reduce gastrointestinal (GI) toxicity from aspirin is the use of enteric-coated or buffered aspirin. Enteric-coated aspirin is designed to resist disintegration in the stomach, dissolving in the more neutral-to-alkaline environment of the duodenum. Although enteric-coated aspirin diminishes endoscopic signs of gastroduodenal injury, it does not protect against the clinically relevant end point of gastrointestinal bleeding [18-22]. In a placebo-controlled Australian/United States study in healthy older adults, enteric-coated aspirin

100 mg per day increased the risk of upper GI bleeding (HR 1.87; 95% CI, 1.32-2.66) without significantly reducing cardiovascular events [22]. These findings are not surprising, since injury severe enough to induce bleeding is thought to reflect the systemic rather than the topical effects of aspirin [23]. The systemic effect of aspirin on the stomach and duodenum also probably explains why buffered aspirin is no more effective than plain aspirin in preventing ulcer bleeding [21]. (See "NSAIDs (including aspirin): Pathogenesis and risk factors for gastroduodenal toxicity".)

Low-dose aspirin for cardiovascular protection — Issues related to bleeding risk of low-dose aspirin for primary cardiovascular protection are also discussed separately. (See "Aspirin in the primary prevention of cardiovascular disease and cancer", section on 'Bleeding'.)

Dual antiplatelet therapy (eg, aspirin and clopidogrel) — Issues related to GI bleeding with dual antiplatelet therapy in patients with cardiovascular disease are discussed separately. (See "Coronary artery disease patients requiring combined anticoagulant and antiplatelet therapy", section on 'Bleeding'.)

ROLE OF HELICOBACTER PYLORI

Multiple studies have evaluated the relationship between *Helicobacter pylori* and the risk of peptic ulcer disease (PUD) in nonsteroidal anti-inflammatory drug (NSAID) users. (See "NSAIDs (including aspirin): Pathogenesis and risk factors for gastroduodenal toxicity".)

Based upon the available evidence, the following is a reasonable approach:

- Patients with a history of uncomplicated or complicated peptic ulcers (gastric, duodenal) should be tested for *H. pylori* prior to beginning a course of NSAID or low-dose aspirin therapy. If present, *H. pylori* should be treated with appropriate therapy, even if it is believed that the prior ulcer was due to NSAIDs.

- In asymptomatic patients with no history of ulcer and not currently taking an NSAID, physicians can consider *H. pylori* testing prior to beginning long-term therapy with a NSAID. A review of this topic suggested that eradication of *H. pylori* was beneficial in patients who were naïve to NSAIDs, while little benefit was observed in patients already taking and tolerating NSAIDs [24]. This "test-and-treat" approach may be more useful in populations with a relatively high prevalence of *H. pylori* infection.

SELECTIVE COX-2 INHIBITORS (COXIBS)

The primary effect of nonsteroidal anti-inflammatory drugs (NSAIDs) is to inhibit cyclooxygenase (COX), thereby impairing the transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. Two isoforms of COX exist: COX-1 and COX-2. COX-1 is constitutive and involved in gastric and duodenal cytoprotection [25], while COX-2 is inducible and involved in inflammation and perhaps healing of gastroduodenal lesions. It has been proposed that the ideal NSAID would inhibit the inducible COX-2 isoform (thereby decreasing tissue inflammation) without having any effect on the COX-l isoform (thereby minimizing gastrointestinal [GI] toxicity) [25,26]. (See "NSAIDs: Pharmacology and mechanism of action" and "Overview of COX-2 selective NSAIDs".)

Clinical trials and meta-analyses have evaluated the gastroduodenal toxicity of coxibs when compared to nonselective NSAIDs [10]. Detailed information regarding these trials is presented elsewhere. These data suggest that coxibs are associated with a reduced risk of gastrointestinal bleeding compared with nonselective NSAIDs but that the risk is increased compared with placebo. Thus, coxibs may be safer than conventional NSAIDs for reduction in the risk of gastrointestinal bleeding but are still associated with an increased risk. (See "COX-2 inhibitors and gastroduodenal toxicity: Major clinical trials".)

Any potential gastroduodenal sparing effect with coxibs may be abrogated when they are used concurrently with low-dose aspirin therapy for prevention of cardiovascular disease [27]. One population-based case control study found that coxibs were associated with a modest reduction in the risk of gastrointestinal bleeding compared with nonselective NSAIDs (RR 0.6, 95% CI 0.4-0.9 among aspirin nonusers) [28]. Concomitant use of aspirin negated the benefit of coxibs.

A case-control study suggested that patients taking warfarin concomitantly with a nonselective NSAID or a coxib have an increased risk of hospitalization for upper gastrointestinal bleeding [29]. The magnitude of risk was similar, suggesting that the coxibs may not be GI-protective in this population.

Coxib usage declined with concerns related to their cardiovascular toxicity. In the Prospective Randomized Evaluation of Celecoxib Integrated Safety (PRECISION) trial in patients with arthritis pain, however, celecoxib was found to be non-inferior to ibuprofen and naproxen with respect to a composite primary cardiovascular endpoint [30]. (See "NSAIDs: Adverse cardiovascular effects".)

PREVENTION STRATEGIES

Options for reducing the risk of gastroduodenal toxicity include (a) using a nonselective nonsteroidal anti-inflammatory drug (NSAID) together with a proton pump inhibitor (PPI) or misoprostol or (b) using a coxib with or without a PPI. The use of high-dose H2 blockers is reserved for patients who cannot tolerate PPIs or misoprostol.

Multiple studies have evaluated a variety of strategies for preventing ulcers in patients requiring NSAIDs. A meta-analysis of 112 randomized controlled trials found no evidence supporting the effectiveness of H2 receptor antagonists at standard doses [31]. However, the risk of symptomatic ulcers was significantly reduced by PPIs (relative risk [RR] 0.09, 95% CI 0.02-0.47) and by misoprostol (RR 0.36, 95% CI 0.02-0.65). Coxibs in place of a nonselective NSAID also reduced risk (RR 0.49, 95% CI 0.38-0.65).

Proton pump inhibitors — PPIs are useful for the prevention of NSAID-induced and low-dose aspirin-induced ulcers [32-38]. The Prospective Randomized Evaluation of Celecoxib Integrated Safety (PRECISION) trial randomized OA or RA patients whose arthritis pain was resistant to acetaminophen and who were at increased risk for cardiovascular disease (nearly one-half taking low-dose aspirin), but who were not at very high risk for ulcer disease (recent ulcer disease was an exclusionary criteria), to receive celecoxib (100 mg bid), ibuprofen (600 mg tid), or naproxen (375 mg bid) as initial NSAID doses to control arthritis pain plus esomeprazole (20 or 40 mg per day in each group). Clinically significant gastrointestinal (GI) events during a median follow up period of 34 months occurred in only 0.7 percent, 0.9 percent, and 0.7 percent of patients, respectively [39]. PPIs are better tolerated than misoprostol [30].

Misoprostol — The risk for NSAID-induced gastric or duodenal ulcer can be decreased with concomitant use of the prostaglandin E analog misoprostol [39]. In the largest trial, 8843 patients with rheumatoid arthritis receiving continuous therapy with any of 10 nonselective NSAIDs were randomly assigned to receive 200 mcg of misoprostol or placebo four times daily for six months [2]. Serious upper GI complications (bleeding, perforation, gastric outlet obstruction) were reduced in patients receiving misoprostol from 0.95 to 0.38 percent, a relative risk reduction of 40 percent, with an absolute risk reduction of 0.57 percent (ie, 175 patients needed to be treated to reduce one complication). However, more patients receiving misoprostol rather than placebo withdrew from the study during the first month (20 versus 15 percent), primarily because of diarrhea and abdominal discomfort. Misoprostol is not tolerated as well as PPIs [31,33].

Doses of misoprostol lower than 200 mcg four times daily have fewer side effects [39]. These lower doses have not received FDA approval, and have not been shown to reduce clinically meaningful ulcer endpoints, however.

PPI (lansoprazole) versus misoprostol

- The efficacies of lansoprazole and misoprostol were compared in a multicenter trial in which 537 patients who were long-term NSAID users were randomly assigned to placebo, misoprostol (200 mcg four times daily), or one of two doses of lansoprazole (15 or 30 mg daily) [33]. After 12 weeks, the 49 percent incidence of endoscopically detected gastroduodenal ulceration with placebo and was significantly reduced with misoprostol (7 percent) and, to a lesser extent, with both doses of lansoprazole (20 and 18 percent, respectively). However, patient withdrawals were more common in the misoprostol group.

PPI (esomeprazole) used with either nonselective NSAIDs or coxibs

Esomeprazole was evaluated for prevention of NSAID-associated ulcers based upon the results of two multicenter trials involving a total of 1429 patients who were taking NSAIDs continuously (nonselective or COX-2 selective, with or without low-dose aspirin).

Patients were at increased risk for peptic ulcer disease (PUD) either because they were older than 60 or had a history of an ulcer. They were randomly assigned to co-therapy with a PPI (20 or 40 mg of esomeprazole) or placebo for six months. All patients were *H. pylori* negative and were free of active ulcer disease at randomization. The primary end point was endoscopically-detected ulcer development [40]. The major findings in both studies were as follows:

- Endoscopic ulcers developed in a similar proportion of patients taking a nonselective NSAID or coxib without esomeprazole (17.1 versus 16.5 percent). This observation underscores that selective COX-2 inhibitors may not protect against endoscopic ulcer formation in these high-risk patients.

- The cumulative proportion of patients developing endoscopic ulcers at six months was significantly reduced with esomeprazole co-therapy (17 percent with placebo versus 5.2 and 4.6 percent with the 20 and 40 mg dose of esomeprazole, respectively).

- The proportion of patients developing endoscopic ulcers who were taking a coxib plus esomeprazole was not significantly different from the proportion taking a nonselective NSAID plus esomeprazole (3 versus 6 percent).

Several important study limitations should be considered. First, only 17 percent of patients had a history of PUD and none had active ulcer disease at randomization and thus the studies focused mainly on primary prophylaxis in elderly patients. Second, patients were not randomized to a nonselective NSAID versus a selective coxib. Thus, patients who were considered to be at higher risk for UD may have been treated with a coxib, possibly accounting

for the high rate of endoscopic ulcer in this group. Third, the studies analyzed patients receiving low-dose aspirin as having received a nonselective NSAID even if they were taking a coxib. Fourth, the studies focused on endoscopic, not clinical, ulcer disease.

Coxib (celecoxib) versus naproxen plus lansoprazole, together with low-dose aspirin

A randomized endoscopic trial in low-dose aspirin users compared celecoxib 200 mg per day with the combination of naproxen 500 mg twice daily and lansoprazole [41]. There was no difference between these two approaches, with gastroduodenal ulcers seen in 10 and 9 percent of patients, respectively.

Coxib (etoricoxib) versus diclofenac

Another randomized controlled trial assessed the cardiovascular toxicity of etoricoxib versus the nonselective NSAID diclofenac [42]. In a pre-specified analysis of GI toxicity, etoricoxib was associated with significantly less gastrointestinal toxicity regardless of PPI or ASA co-administration. This benefit held true only for uncomplicated GI events; there was no difference between the two groups for complicated GI events [42].

Nonselective NSAID with either a PPI or misoprostol versus a coxib

Data are conflicting about whether coxibs provide additional protection compared with conventional, nonselective NSAIDs that are combined with either a proton pump inhibitor or misoprostol:

- In a randomized trial of 4484 patients with osteoarthritis or rheumatoid arthritis, 2238 patients were assigned to receive celecoxib and 2246 patients were assigned to receive diclofenac plus omeprazole [43]. Patients in the celecoxib arm were significantly less likely to develop GI toxicity compared with patients in the diclofenac/omeprazole arm (1 versus 4 percent, hazard ratio 4.3).

- A population based study compared 1382 patients with upper gastrointestinal complications who were taking a conventional NSAID or a coxib with 22,957 age- and sex-matched controls [44]. Co-therapy with a PPI or misoprostol or use of a coxib all significantly reduced the risk of upper gastrointestinal complications. COX-2 inhibitor use was not more likely to lower complications compared with PPIs but were superior to low-dose misoprostol. The combination of a coxib with a PPI was associated with a greater reduction in risk (adjusted OR 0.36 (95% CI 0.28-0.47) as compared to an OR of 0.67 (95% CI 0.48-0.95) for a PPI plus a conventional, nonselective NSAID.

The issue of using a coxib plus a PPI compared to a nonselective NSAID plus a PPI in patients at increased risk for PUD remains unsettled. The former approach is probably non-inferior but may not be superior [30]. Furthermore, the PPI rabeprazole was associated with more celecoxib-related small intestinal mucosal injury (mostly erosions as opposed to ulcers) than placebo plus celecoxib [45], although the clinical significance of this observation is unknown.

H2 receptor antagonists — Standard doses of H2 receptor antagonists were not effective for the prevention of NSAID-induced gastric ulcers in most reports, although they may prevent duodenal ulcers [46]. Studies that detected a benefit on gastric ulcer prevention were short-term (12 to 24 weeks) and focused on endoscopic rather than clinical endpoints [47,48].

High-dose H2 receptor antagonists have also been studied. Again, the trials were short-term and focused on endoscopic endpoints. In two randomized trials (REDUCE-1 and REDUCE-2), patients who required daily NSAIDs for at least six months were assigned to receive either ibuprofen 800 mg plus famotidine 26.6 mg or ibuprofen 800 mg three times per day [49]. The outcome of interest was ulcer development over 24 weeks of treatment. The pooled analysis of the two studies comparing the drug combination with ibuprofen alone found that the combination significantly reduced overall upper gastrointestinal ulcer development (14 versus 24 percent), gastric ulcer development (13 versus 21 percent), and duodenal ulcer development (2 versus 7 percent).

Aspirin-phosphatidylcholine combination — A study in healthy volunteers between the ages of 50 and 74 found that combining 325 mg aspirin per day with phosphatidylcholine reduced a combined endoscopic endpoint (petechiae, erosions, ulcers) compared with aspirin alone [50].

Potassium-competitive acid blocker — A novel agent, vonoprazan, has been shown to be non-inferior to the PPI lansoprazole in a double-blinded, randomized controlled study for the secondary prevention of NSAID-associated peptic ulcers [51]. Vonoprazan has been approved for use in Japan but is not available worldwide.

MONITORING PATIENTS TAKING NSAIDS

Monitoring patients while on NSAIDs can be difficult since many patients who develop GI toxicity are asymptomatic until shortly before the adverse event occurs. An NSAID-induced gastrointestinal complication should be suspected if the patient develops unexplained blood loss anemia, iron deficiency, significant dyspepsia, or exhibits overt GI bleeding. The appropriate test to order is upper gastrointestinal endoscopy, unless ulcer perforation is

suspected in which case computed tomography scan of the abdomen should be ordered immediately.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: NSAID-related ulcer complications" and "Society guideline links: Peptic ulcer disease".)

SUMMARY AND RECOMMENDATIONS

As noted above, multiple studies have evaluated a variety of strategies for preventing ulcers in patients requiring prolonged nonsteroidal anti-inflammatory drugs (NSAIDs) or low-dose aspirin for cardiovascular protection. The following represents recommendations based upon the available data and expert consensus.

- The risk of gastroduodenal toxicity is related to risk factors described above, the patient's *Helicobacter pylori* (*H. pylori*) status, and the specific type and dose of NSAID. Significant gastrointestinal (GI) toxicity generally does not begin for several weeks, although it can appear as early as day 7 with some NSAIDs such as indomethacin or ketorolac. (See 'Risk factors' above.)

- The ability to modify the risk depends upon the clinical setting. As noted above, patients with a history of uncomplicated or complicated peptic ulcers (gastric, duodenal) should be tested for *H. pylori* prior to beginning long-term use of an NSAID or low-dose aspirin. If present, *H. pylori* should be treated with appropriate therapy, even if it is believed that the prior ulcer was due to NSAIDs. (See 'Role of helicobacter pylori' above.)

- Attempts should be made to use the lowest dose and shortest duration of NSAID treatment that is feasible. While it is preferable to use NSAIDs with the lowest potential for GI toxicity, all NSAIDs are associated with an increased GI risk.

- In asymptomatic patients with no history of ulcer and not currently taking an NSAID, physicians can consider *H. pylori* testing prior to beginning long-term therapy with a NSAID. It is possible that successfully treating *H. pylori* infection in such individuals will reduce the risk of NSAID-related ulcer complications, but additional studies of this approach are needed. This "test-and-treat" approach may be more useful in populations with a relatively high prevalence of *H. pylori* infection. In patients with a history of peptic

ulcer disease or ulcer complications requiring an NSAID or low-dose aspirin, we recommend testing for *H. pylori* and treating for *H. pylori* if positive (**Grade 1A**). (See "NSAIDs (including aspirin): Secondary prevention of gastroduodenal toxicity".)

- For patients who have multiple risk factors for NSAID-related gastroduodenal toxicity, options include therapy with a coxib or a nonselective NSAID in combination with a proton pump inhibitor (PPI) or misoprostol. High-dose H2 receptor antagonists are reserved for patients who cannot tolerate PPIs or misoprostol. (See 'Risk factors' above and 'Selective COX-2 inhibitors (COXIBS)' above and 'Proton pump inhibitors' above.)

- We recommend co-administration of a PPI in patients who require an NSAID and are at high or moderate risk for GI toxicity (**Grade 1B**). (See 'Risk factors' above.) We prefer PPIs to other preventive approaches because of their convenience and relatively good safety profile.

- The approved doses of these ulcer prevention drugs in patients taking nonselective NSAIDs include misoprostol (200 mcg four times daily), lansoprazole (15 or 30 mg daily), and esomeprazole (20 or 40 mg daily). Although not all PPIs have received FDA approval, they probably all have similar effectiveness.

- If a coxib is used, it is important to realize that any GI protective effect may be eliminated or reduced with the concomitant use of low-dose aspirin for cardiovascular prophylaxis. (See 'Coxib (celecoxib) versus naproxen plus lansoprazole, together with low-dose aspirin' above.)

- An NSAID-induced gastrointestinal complication should be suspected if the patient develops unexplained blood loss anemia, iron deficiency, severe dyspepsia, or exhibits overt GI bleeding. Patients who develop NSAID-induced non-ulcer dyspepsia may respond to H2 receptor antagonists or PPIs at standard doses, but of these choices only PPIs also reliably reduce the risk of NSAID-induced ulcer or its complications. Development of dyspepsia may signal that an ulcer has developed at which point an upper endoscopy can be considered. Switching to a different NSAID or to a coxib may eliminate dyspepsia and obviate the need for an H2 antagonist or PPI. Misoprostol does not reduce, and may even increase, dyspeptic symptoms. (See 'Monitoring patients taking NSAIDs' above and 'Misoprostol' above.)

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