Gastrointestinal safety and tolerability of nonselective nonsteroidal anti-inflammatory agents and cyclooxygenase-2–selective inhibitors

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■ **ABSTRACT**

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used of all drugs and are the most common medications used by persons aged 65 years or more. NSAIDs have a number of side effects, of which the most prevalent and serious is gastrointestinal (GI) toxicity. GI side effects of NSAIDs range from dyspepsia and gastroduodenal ulcers to serious, potentially fatal GI complications including bleeding and perforation. Serious GI complications often lack warning signs; knowledge of risk factors for NSAID-related gastropathy can identify patients at high risk, allowing for initiation of the appropriate therapeutic intervention. Risk factors include advanced age, NSAID dose, prior GI complications, infection with *Helicobacter pylori*, and use of corticosteroids and anticoagulants. There are few well-established strategies to prevent GI complications in NSAID users. Risk assessment and cotherapy with acid suppressors (H_2-receptor antagonists and proton pump inhibitors) or prostaglandin replacement (misoprostol) and *H pylori* eradication are beneficial. Cyclooxygenase-1 (COX-1) is a key enzyme in gastroprotective mucosal defenses, and the best way to prevent GI toxicity is to avoid drugs that inhibit COX-1. Clinical studies of the COX-2–selective inhibitors rofecoxib and celecoxib have demonstrated efficacy equivalent to nonselective NSAIDs with lower rates of GI side effects (for example, incidence of endoscopic ulcers equivalent to placebo). Selective COX-2 inhibitors (coxibs) provide effective treatment of pain and inflammation while reducing risk of gastropathy.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used of all drugs. It is estimated that 1% to 2% of the world population takes at least 1 aspirin tablet daily, and in the United States alone 20 to 30 billion tablets are purchased each year.[1,2] NSAIDs are among the medications most commonly used by persons aged 65 years or more.[3] Though effectively addressing pain and inflammation, nonselective NSAIDs are associated with several untoward side effects including gastric intolerance, gastric ulceration, inhibition of platelet function, and alterations in renal function.[4]

The most prevalent and significant adverse outcomes of NSAID use are gastrointestinal (GI) ulcer-

Safety of nonselective NSAIDs and coxibs

Gastrointestinal (GI) side effects of nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) due to cyclooxygenase-1 (COX-1) inhibition are responsible for significant morbidity and mortality

Epidemiologic and clinical studies have identified important risk factors for NSAID-related gastropathy; namely, advancing age, high NSAID dose, prior GI complications, *Helicobacter pylori* infection, and use of anticoagulants or corticosteroids

The incidence of GI complications can be reduced by risk assessment and risk-reduction strategies

Small trials and observational studies show that *H pylori* eradication and cotherapy with prostaglandin replacement and acid suppression reduce risk of serious GI complications

The selective COX-2 inhibitors rofecoxib and celecoxib (coxibs) have efficacy equivalent to nonselective NSAIDs with no new unexpected side effects

ation and serious GI complications such as perforation and bleeding.[2,5] Estimates show that in the United States approximately 107,000 patients are hospitalized each year for NSAID-related GI complications and 16,500 NSAID-related deaths occur in arthritis patients alone.[6] In a prospective study of more than 11,000 patients with osteoarthritis (OA) or rheumatoid arthritis (RA), risk of hospitalization due to serious NSAID-related GI complications was 2.5 to 5.5 times greater than that of the general population.[6] The mortality rate among patients hospitalized for serious NSAID-related bleeding complications is 10% to 15%.[5] There are often no warning signs for serious GI complications, and prospective studies show that more than 80% of patients with these complications had no previous GI illness.

Upper GI symptoms, ulcers, and ulcer complications due to NSAID use are a significant cause of morbidity and mortality. Approximately 25% of NSAID users will have endoscopic lesions of at least 3 mm in the gastric mucosa, and 1% to 4% of patients using NSAIDs will have symptomatic ulcers or ulcer complications.[6] The mortality rate attributed to NSAID-related GI toxicity is 0.2% per year with an annual relative risk of 4.21 compared with NSAID nonusers.[2]

NSAID-related morbidity and mortality come at a high price to society in both human and economic terms. It is estimated that each NSAID-related hospitalization costs an average of $15,000 to $20,000, with annual direct medical costs of these complications exceeding $2 billion in the United States alone.[2] Among those aged 65 years or more, costs have been estimated to be $500 million per year.[3]

GASTROINTESTINAL RISK AND NSAIDs

NSAID-associated gastropathy

NSAIDs have the common property of treating fever, pain, and inflammation by inhibiting synthesis of prostaglandins. NSAIDs bind reversibly or irreversibly (in the case of aspirin) to cyclooxygenase (COX) enzymes (**Figure 1**). COX-1–derived prostaglandins are responsible for mucosal defense and cytoprotection in the GI tract, while COX-2–derived prostaglandins mediate inflammation, pain, and fever. Most NSAIDs are nonselective, blocking both COX-1 and COX-2 isoenzymes. Deleterious effects of nonselective NSAIDs on gastroprotection result from their inhibition of COX-1.[2] With the development of COX-2–selective inhibitors, it has been possible to achieve the level of clinical efficacy of nonselective NSAIDs without the GI-toxic effects associated with COX-1 inhibition.

There are three levels of gastric mucosal defense relevant to gastric toxicity of NSAIDs caused by COX-1 inhibition (**Figure 2**). The first line of gastric defense is the mucous gel, which protects against the acidic contents of the gastric lumen. Surface epithelial cells, which can withstand pH as low as 2.5, provide the second line of gastric defense. Finally, the postepithelial barrier prevents deep mucosal damage because of the buffering effect of bicarbonate release by parietal cells; mucosal blood flow also removes damaging H^+.[1] Prostaglandin inhibition resulting from the blocking of COX-1 affects all three defense mechanisms by causing decreases in epithelial mucus production, bicarbonate secretion, mucosal blood flow, and epithelial proliferation.[2] Diminished mucosal protection makes the GI tract vulnerable to the endogenous insults of gastric acid, bile, and enzymes, and may enhance damage by exogenous factors, such as alcohol and other injurious agents.

The clinical scope of NSAID-related GI injury ranges from self-limited dyspepsia to ulcers, gastroduodenal hemorrhage, perforation, and death. Erosions are superficial, limited to the mucosal layer, whereas ulcers penetrate to the level of the submucosa. GI injury is usually assessed by endoscopic examination and is based on subjective mea-

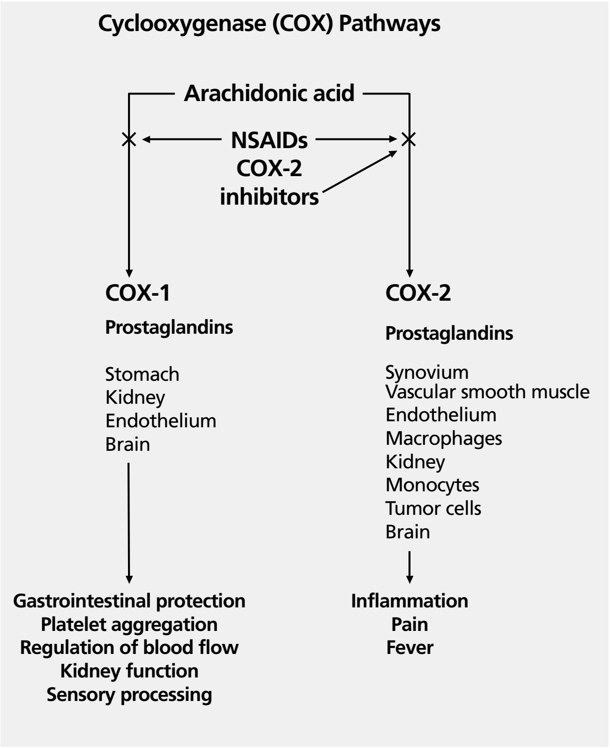


FIGURE 1. Mechanisms of NSAID-induced injury and potential sites for pharmacologic strategies for prevention of GI toxicity.[2]

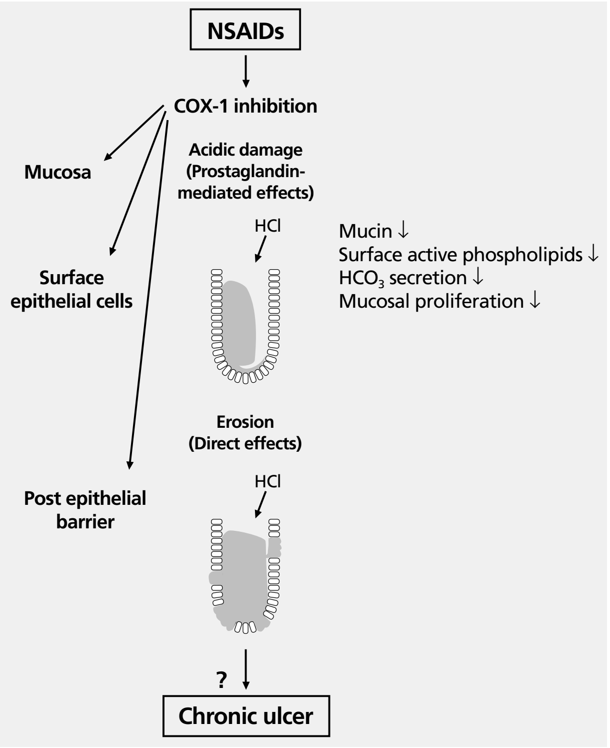


FIGURE 2. COX-1 inhibition and GI toxicity. (Adapted from Scheiman[1] with permission.)

sures such as the size and depth of the lesion. A size of 3.0 mm and some observable depth are usually employed in clinical trials to differentiate between erosions and ulcers. Histologic examination has been used to confirm endoscopic findings. Biopsy can reveal gastric mucosal injury and inflammation associated with *Helicobacter pylori* infection or focal injury and acute inflammation associated with NSAID damage.[7] Damage to the gastric epithelium is seen within minutes of NSAID ingestion, and erosions can be detected endoscopically within hours.[8] The relation of endoscopic lesions to resulting GI hemorrhage and perforations, however, is unclear. For this reason, the best measures of the clinical effect of NSAIDs on gastric mucosa are long-term endoscopic and clinical trial data.[9]

Risk assessment

Knowledge of risk factors for NSAID-associated gastropathy offers a means to identify patients at high risk. Bleeding and perforation often occur without warning and are associated with a high mortality rate. In the absence of cautionary signs of serious complications, it is important to define risk factors that can initiate appropriate therapeutic intervention. A number of epidemiologic and clinical studies have examined risk factors using case-control, retrospective studies, prospective cohort analyses, and meta-analysis methodologies. These studies have consistently identified a number of risk factors for serious GI complications, including advanced age,[10–14] higher NSAID dose,[15–17] prior serious GI complications or hospitalization,[11–13,18,19] anticoagulant use,[10,19,20] corticosteroid use,[11,12,19,21] and current or previous NSAID use.[10,11,13,15,19–21] Results of epidemiologic studies examining risk associated with gender or alcohol and tobacco use have been less consistent.[6] While most studies have compared relative risks in various subgroups (eg, aged <60 years vs aged ≥60 years, etc), the magnitude of absolute risk of NSAID use is clinically relevant.[17]

The greatest risk of developing a serious GI complication occurs in the first 30 days of use. In a meta-analysis of 16 studies, it was found that with less than 1 month of NSAID exposure the odds ratio (OR) for a serious GI event was 8.00 (95% confidence interval [CI], 6.37–10.06). For longer than 1 month but less than 3 months' exposure, the OR decreased to 3.31 (95% CI, 2.27–4.82), and to 1.92 (95% CI, 1.19–3.13) for NSAID exposure longer than 3 months.[12] While risk is highest early in exposure, prospective studies have shown that risk is a persistent feature of NSAID use. The Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) study followed 1,600 patients from the onset of NSAID use and found that risk remained constant over a 10-year follow-up, suggesting that there is not a mucosal adaptation to NSAIDs.[6]

Age is one of the strongest predictors of NSAID-related GI complications, and most studies defined older age as greater than 60 years. ARAMIS, which has followed clinical outcomes prospectively in over 11,000 patients, showed that risk of hospitalization for NSAID-related GI complications increases by approximately 4% per year of age.[6]

All nonselective NSAIDs are associated with a similar spectrum of GI complications, and the relative risk of NSAID use compared with nonuse is fairly uniform across case-control and prospective studies for the various drugs examined. In ARAMIS, toxicities of 12 different NSAIDs were examined, and the majority of agents had a similar degree of toxicity.[6] In this study, ibuprofen was least toxic, whereas ketoprofen and indomethacin were most toxic. It is important to note that the toxicity of aspirin even at low doses is clinically relevant. Aspirin use resulted in significant increased absolute risk of GI bleeding at doses as low as 75 mg/d[22,23] and without evidence of the dose response seen with other nonselective NSAIDs. In a meta-analysis of 24 randomized trials involving nearly 66,000 participants, the incidence of GI hemorrhage was similar in patients taking low or high doses of aspirin (2.47% vs 2.30% for >163 mg/day and <163 mg/day, respectively).[24] In the United Kingdom Transient Ischemic Attacks trial, however, the prospective examination of 2,435 patients receiving placebo, aspirin 300 mg/day, or aspirin 600 mg twice daily demonstrated a greater risk of GI ulcer bleeding with the higher aspirin dose.[25] Furthermore, there is no evidence that the use of buffering or enteric coating of aspirin decreases this risk.[23,24,26]

Risk reduction

There are currently few well-established strategies for the prevention of ulcers and GI bleeding in patients taking NSAIDs. The best way to prevent the adverse effects of NSAIDs is to avoid the use of nonselective drugs that block COX-1. In addition, alternative analgesics such as acetaminophen (paracetamol) carry a very low risk of causing ulcers.[27] Patients taking nonselective NSAIDs who are at high risk for GI complications should be considered for cotherapy with a mucosal protective agent.

The ability of various cotherapeutic agents to reduce the incidence of nonselective NSAID-induced GI ulcers has been examined. In endoscopic studies, the H_2-receptor antagonists cimetidine and ranitidine and the surface active agent sucralfate showed no benefit in preventing NSAID-related gastric ulcers compared with placebo.[28–30] H_2-receptor antagonists may have some protective effect on the duodenum, and famotidine in large doses (40 mg twice daily) reduced the cumulative incidence of gastric ulcers.[31,32]

Proton pump inhibitors (PPIs) are potentially more effective acid suppressors than high-dose H_2-receptor antagonists. For patients with difficult-to-treat acid-related disorders, PPIs may be the drugs of choice, especially with the advent of newer-generation agents of this class.[33] Lansoprazole is useful for managing acid-related disorders and is currently the only PPI approved by the US Food and Drug Administration (FDA) for the prevention and treatment of NSAID-induced injury.[34–36]

Two large trials have examined another PPI, omeprazole, for secondary prevention of chronic ulcers: the Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management (OMNIUM) trial, and the Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment (ASTRONAUT).[37,38] In both studies, omeprazole was shown to be superior to placebo for ulcer healing and in the prevention of relapse. More patients receiving omeprazole were in remission at 6 months compared with those receiving misoprostol and ranitidine; these comparator drugs were used at suboptimal doses, however.[39]

Misoprostol is a prostaglandin analog that is also approved by the FDA for the prevention of NSAID-induced ulcers. Misoprostol acts as both an antisecretory agent and as a replacement for mucosal prostaglandin deficiency due to the inhibition of COX-1 by NSAIDs.[39] The Misoprostol Ulcer Complications Outcomes Study Assessment (MUCOSA) examined over 8,800 patients with RA in a randomized, double-blind trial of 200 μg misoprostol four times daily compared with placebo. GI complications were assessed clinically, not endoscopically. Overall, the incidence of serious upper GI complications was approximately 40% lower in patients receiving misoprostol but there was no significant reduction in GI bleeding.[14] In an earlier trial of 638 patients, the same misoprostol regimen resulted in a significant decrease in the incidence of the endoscopic endpoints of duodenal and gastric ulcers.[40] In both studies, misoprostol reduced but did not entirely eliminate ulcers or complications, and the mortality rates were similar in the misoprostol and placebo groups. Misoprostol is relatively poorly tolerated, causing diarrhea and abdominal pain. In MUCOSA, significantly more participants in the misoprostol group than the placebo group withdrew from the study as a result of adverse GI events, and nearly 30% of those in the active arm of the study group could not take the full dose of misoprostol also because of side effects.[14] Health economic studies show that misoprostol is cost-effective only for high-risk patients.[41,42]

A recent meta-analysis of controlled clinical trials evaluating the ability of H_2-receptor antagonists, PPIs, and misoprostol to prevent NSAID-related GI damage found that strategies utilizing these agents were effective for short-term prevention of NSAID-related damage.[43] PPIs and misoprostol were more effective than H_2-receptor antagonists in preventing such NSAID-induced injury. Notably, this benefit was more pronounced in healthy subjects than in patients with arthritis, highlighting the need for agents that may minimize NSAID-related injury in this patient population.

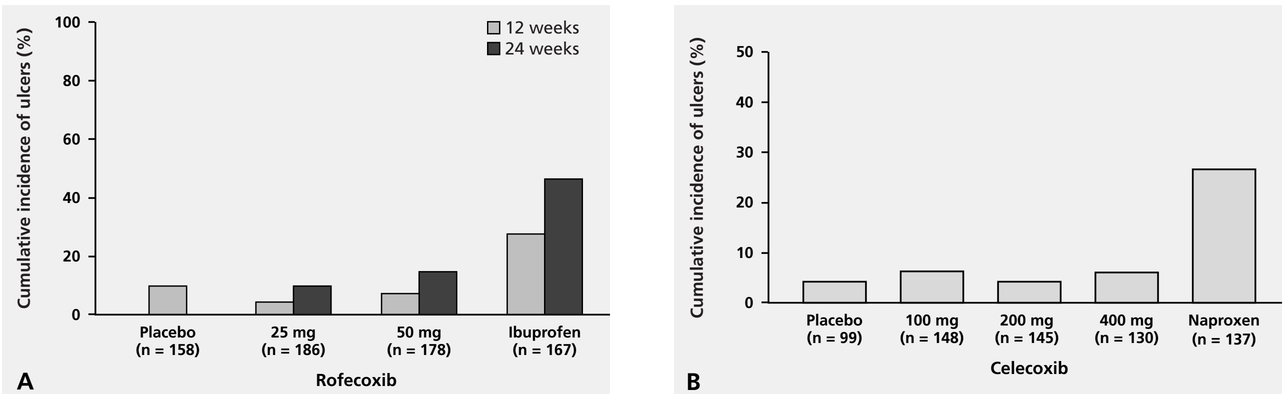
The relation of *H pylori* to NSAID-associated ulcer and ulcer complications remains controversial. NSAIDs and *H pylori* contribute to ulcer formation by different mechanisms, but it is not possible to distinguish whether an ulcer is caused by NSAIDs, *H pylori*, or both.[44] In patients using NSAIDs, it remains unclear whether *H pylori* infection is an independent risk factor, or whether *H pylori* infection and NSAID use interact in an additive manner. A history of ulcers is known to greatly increase GI risk associated with NSAID use. Several studies suggest that the presence of *H pylori* infection may be associated with an increased incidence of duodenal ulcers in NSAID users.[31,32,45–48] A meta-analysis evaluating the impact of *H pylori* and NSAID use on the risk of peptic ulcer disease suggested that NSAIDs and *H pylori* have additive/interactive effects.[49] While the incidence of peptic ulcers was higher with NSAID use alone (25% vs 5.5%, NSAID-takers and non-NSAID takers, respectively; OR = 5.7 among *H pylori*-negative subjects), the presence of *H pylori* was associated with even higher incidences in both groups. In *H pylori*-positive subjects, the incidence of peptic ulcer was 49.2% among NSAID takers compared with 26% in non-NSAID-takers. Notably, presence of both *H pylori* and NSAID use was associated with an OR = 16.5 compared with absence of *H pylori* and non-NSAID use.[49]

The eradication of *H pylori* is possible, and treatment of infection in NSAID users could decrease risk of ulcers. One study compared the benefit of *H pylori* eradication in secondary prevention with the benefit of PPI cotherapy by examining the prevention of recurrence of upper GI bleeding in patients with *H pylori* infection who were taking NSAIDs.[50] Patients taking 80 mg of aspirin daily or 500 mg of naproxen twice daily were randomized to receive either 20 mg of omeprazole daily or *H pylori* treatment consisting of bismuth subcitrate, tetracycline, and metronidazole. In patients taking aspirin, the eradication of *H pylori* led to a decrease in recurrent GI bleeding that was equivalent to treatment with omeprazole. For patients taking naproxen, omeprazole cotherapy was superior to *H pylori* eradication for secondary prevention of upper GI bleeding.[50]

■ SAFETY AND TOLERABILITY OF COX-2–SELECTIVE INHIBITORS

Clinical results

Given the risk of GI complications associated with NSAID use and the limitations of cotherapies such as misoprostol and acid-suppression therapy for primary and secondary prevention, the use of COX-1–sparing drugs has a critical role in treatment of pain and inflammation. Prospective studies have shown that selective COX-2 inhibitors are associated with lower risk of GI adverse events than NSAIDs that inhibit both COX-1 and COX-2. These studies demonstrate the ability of COX-2–selective agents to provide efficacy equivalent to nonselective NSAIDs while reducing the three main categories of GI events, namely, adverse GI symptoms (nausea, vomiting, abdominal pain); mucosal lesions (as shown by endoscopy or x-ray); and serious GI complications (bleeding, perforation, and obstruction).[6]



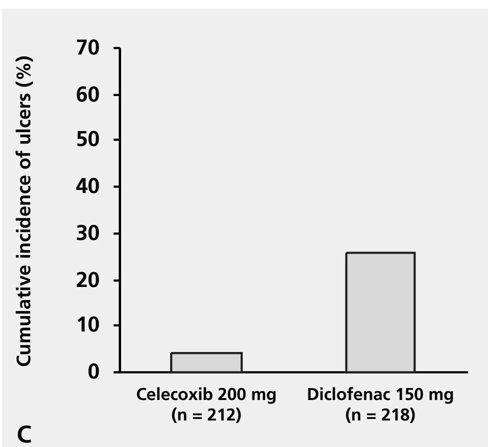


FIGURE 3. (A) Cumulative incidence of gastroduodenal ulcers at 12 and 24 weeks in osteoarthritis patients randomized to rofecoxib 25 and 50 mg/day, ibuprofen 2,400 mg/day, or placebo[52] (Adapted with permission from Laine et al. A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. Osteoarthritis Endoscopy Study Group. Gastroenterology 1999; 117:776-783.); (B) in patients at 12 weeks after being randomized to celecoxib 100, 200, and 400 mg twice daily, naproxen 500 mg twice daily, or placebo[53] (Adapted with permission from Simon et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis. A randomized controlled trial. JAMA 1999; 282:1921-1928. Copyrighted 1999, American Medical Association.); and (C) in a 24-week study comparing celecoxib 200 mg twice daily to diclofenac SR 150 mg/day[54] (Adapted with permission from Emery et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. Lancet 1999; 354:2106-2111. Copyright by The Lancet Ltd. 1999.).

Gastrointestinal symptoms ranging from heartburn, nausea, and abdominal pain, so-called nuisance symptoms, to more serious GI complications occur in more than one third of patients taking NSAIDs.[6,18] These symptoms have no demonstrated correlation with endoscopic or clinically relevant events but are important to the quality of life of patients who use NSAIDs. To evaluate such quality-of-life effects, a meta-analysis of the GI adverse events among 5,435 patients enrolled in eight randomized, double-blind trials of rofecoxib was undertaken. In this analysis, the 6-month cumulative incidence of dyspeptic side effects in patients receiving 12.5, 25, or 50 mg of rofecoxib daily was significantly lower than in those receiving nonselective NSAIDs (ibuprofen, diclofenac, or nabumetone).[51] While the cumulative incidence of symptoms in the two groups converged at 12 months, the rate of discontinuation due to adverse GI events in those patients taking NSAIDs continued to be about 30% higher than that of patients taking rofecoxib. The VIOXX Gastrointestinal Outcomes Research (VIGOR) trial examined safety and efficacy of rofecoxib in 8,076 patients.[47] This study showed that incidences of the leading five GI nuisance symptoms were similar for both rofecoxib and naproxen (dyspepsia, abdominal pain, epigastric discomfort, and heartburn). Again in the rofecoxib group, significantly fewer patients discontinued treatment as a result of any one of these symptoms than did patients in the naproxen group (3.5% vs 4.9%). The Celecoxib Long-term Arthritis Safety Study (CLASS), another large GI-outcomes study carried out in patients with OA or RA, demonstrated similar results with celecoxib.[18] The most commonly reported GI symptoms in this study were dyspepsia, abdominal pain, diarrhea, nausea, and constipation. With the exception of diarrhea, the incidence of these events was significantly lower with celecoxib than with the comparator nonselective NSAIDs. For individual NSAIDs, rates of dyspepsia, abdominal pain, and nausea in patients receiving celecoxib were similar to those for ibuprofen and significantly less than those for diclofenac. The CLASS publication[18] reported limited data, out to 6 months. The full 9-month (median follow-up) data were reported in February 2001 and are available at http://www.fda.gov/ohrms/dockets/ac/01/briefing/367761_01_searle.pdf (FDA website address).

Prospective studies have shown that COX-2–selective inhibitors are associated with less frequent incidence of endoscopic ulcers than are nonselective NSAIDs. Rofecoxib was compared with ibuprofen and placebo in a randomized clinical trial in 742 patients with OA.[52] At 12 and 24 weeks, the cumulative incidence of gastroduodenal ulcers of at least 3 mm with rofecoxib (25 or 50 mg once daily) was significantly lower than with ibuprofen (800 mg 3 times daily) and statistically equivalent to placebo (**Figure 3A**). A similar 12-week trial compared the cumulative incidence of gastroduodenal ulcers of at least 3 mm with celecoxib (100, 200, or 400 mg), naproxen (500 mg twice daily), or placebo in 1,149 patients with RA.[53] The incidence of ulcers with all doses of celecoxib was similar to placebo and significantly lower than with naproxen (**Figure 3B**). Another 24-week randomized trial compared celecoxib (200 mg twice daily) with diclofenac SR (150 mg daily) in 655 patients with RA. This trial showed significantly lower incidence of gastroduodenal ulcers in patients receiving celecoxib compared with diclofenac (**Figure 3C**).[54] Long-term outcomes studies of rofecoxib and celecoxib confirm the clinical tolerability and safety of these agents.[18,47] (See article by Scheiman in this supplement.)

SAFETY OF AGENTS IN DEVELOPMENT

Newer COX-2–selective agents also have demonstrated improved GI safety. One such agent, etoricoxib, is being evaluated for the treatment of OA, RA, and chronic lower back pain. An analysis of eight randomized, double-blind, phase II–III efficacy trials (N = 2,651) of this COX-2–selective inhibitor showed significantly fewer (43% less) treatment discontinuations due to NSAID-type symptoms or GI symptoms in general compared with nonselective NSAIDs.[55] A similar analysis of all phase II–III trials (n = 3,123) found that etoricoxib significantly reduced the incidence of investigator-reported and confirmed upper-GI perforations, ulcers, and bleeds by approximately 50% compared with treatment with nonselective NSAIDs (diclofenac, ibuprofen, naproxen).[56] Further trials will help to fully characterize the potential benefits and GI safety and tolerability of etoricoxib.

CLINICAL STRATEGIES TO REDUCE NSAID-RELATED GASTROPATHY

There are several strategies that healthcare providers can employ to decrease the risk of NSAID-related GI complications:

- Risk assessment with special management of those at increased risk should guide clinical strategies
- Risk factors should be modified when possible; eradication of *H pylori* may decrease long-term risk of gastroduodenal ulcers
- As recommended by the practice guidelines of the American College of Rheumatology, a non-NSAID such as acetaminophen (paracetamol) with low GI toxicity should be used as the first line of analgesic therapy
- When a nonselective NSAID is used, the lowest effective dosage is recommended. Although large long-term trials are lacking, there is evidence that some NSAIDs such as nabumetone, etodolac, and meloxicam may be among the more tolerable nonselective NSAIDs
- Cotherapy with an acid-suppressing agent such as a PPI or possibly misoprostol should be considered. This may reduce risk for patients with a history of ulcer bleeding, including those free of *H pylori* infection
- COX-2–selective inhibitors can be used to significantly decrease risk of GI toxicity.

CONCLUSIONS

NSAIDs are responsible for significant morbidity and mortality with high associated direct and indirect costs. Although serious GI complications in NSAID users often have no specific warning signs, patients at high risk for NSAID-related gastropathy have recognizable risk factors. Selective COX-2 inhibitors have efficacy equivalent to that of nonselective NSAIDs with no new unexpected side effects. Rates of dyspepsia reported in patients receiving COX-2 inhibitors in clinical trials were similar to those for nonselective NSAIDs; however, discontinuation rates for dyspeptic symptoms were lower with COX-2 inhibitors than with comparator NSAIDs. Endoscopic damage in patients taking COX-2–selective inhibitors was equivalent to placebo even when coxibs were administered at high dosages. The development and application of COX-2–selective agents is a significant advance, as these agents have overcome one of the major obstacles of NSAID therapy—the risk of ulcers and their potentially fatal complications. In reducing the risk of NSAID-related gastropathy, these drugs also provide an avenue for cost reduction by controlling the economic burden of these complications. In conclusion, coxibs, the selective COX-2 inhibitors, offer a well-tolerated and cost-effective addition to the armamentarium available for the treatment of patients with arthritis.

REFERENCES

1. **Scheiman JM.** NSAIDs, gastrointestinal injury, and cytoprotection. Gastroenterol Clin North Am 1996; 25:279–298.
2. **Wolfe MM, Lichtenstein DR, Singh G.** Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med 1999; 340:1888–1899.
3. **Smalley WE, Griffin MR, Fought RL, Ray WA.** Excess costs from gastrointestinal disease associated with nonsteroidal anti-inflammatory drugs. J Gen Intern Med 1996; 11:461–469.
4. **Weissmann G.** NSAIDS: aspirin and aspirin-like drugs. In: Goldman L, Bennett JC, editors. Cecil Textbook of Medicine. Philadelphia: W.B. Saunders, 2000:114–118.
5. **Singh G, Triadafilopoulos G.** Epidemiology of NSAID induced gastrointestinal complications. J Rheumatol 1999; 26 (suppl 56):18–24.
6. **Singh G.** Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. Am J Med 1998; 105:31S–38S.
7. **Laine L.** Nonsteroidal anti-inflammatory drug gastropathy. Gastrointest Endosc Clin North Am 1996; 6:489–504.
8. **Graham DY, Smith JL.** Aspirin and the stomach. Ann Intern Med 1986; 104:390–398.
9. **Lipsky LPE, Abramson SB, Crofford L, DuBois RN, Simon LS, van de Putte LBA.** The classification of cyclooxygenase inhibitors. J Rheumatol 1998; 25:2298–2303.
10. **Carson JL, Strom BL, Soper KA, West SL, Morse ML.** The association of nonsteroidal anti-inflammatory drugs with upper gastrointestinal tract bleeding. Arch Intern Med 1987; 147:85–88.
11. **Fries JF, Williams CA, Bloch DA, Michel BA.** Nonsteroidal anti-inflammatory drug-associated gastropathy: incidence and risk factor models. Am J Med 1991; 91:213–222.
12. **Gabriel SE, Jaakkimainen L, Bombardier C.** Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. Ann Intern Med 1991; 115:787–796.
13. **Gutthann SP, García Rodríguez LA, Raiford DS.** Individual nonsteroidal antiinflammatory drugs and other risk factors for upper gastrointestinal bleeding and perforation. Epidemiology 1997; 8:18–24.
14. **Silverstein FE, Graham DY, Senior JR, et al.** Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1995; 123:241–249.
15. **Griffin MR, Piper JM, Daugherty JR, Snowden M, Ray WA.** Nonsteroidal antiinflammatory drug use and increased risk for peptic ulcer disease in elderly persons. Ann Intern Med 1991; 114:257–263.
16. **Langman MJ, Weil J, Wainwright P, et al.** Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994; 343:1075–1078.
17. **Hallas J, Lauritsen J, Villadsen HD, Gram LF.** Nonsteroidal anti-inflammatory drugs and upper gastrointestinal bleeding, identifying high-risk groups by excess risk estimates. Scand J Gastroenterol 1995; 30:438–444.
18. **Silverstein FE, Faich G, Goldstein JL, et al.** Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000; 284:1247–1255.
19. **García Rodríguez LA, Jick H.** Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994; 343:769–772.
20. **Shorr RI, Ray WA, Daugherty JR, Griffin MR.** Concurrent use of nonsteroidal anti-inflammatory drugs and oral anticoagulants places elderly persons at high risk for hemorrhagic peptic ulcer disease. Arch Intern Med 1993; 153:1665–1670.
21. **Piper JM, Ray WA, Daugherty JR, Griffin MR.** Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991; 114:735–740.
22. **Weil J, Colin-Jones D, Langman M, et al.** Prophylactic aspirin and risk of peptic ulcer bleeding. BMJ 1995; 310:827–830.
23. **Sørensen HT, Mellemkjær L, Blot WJ, et al.** Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. Am J Gastroenterol 2000; 95:2218–2224.
24. **Derry S, Loke YK.** Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. BMJ 2000; 321:1183–1187.
25. **Slattery J, Warlow CP, Shorrock CJ, Langman MJS.** Risks of gastrointestinal bleeding during secondary prevention of vascular events with aspirin—analysis of gastrointestinal bleeding during the UK-TIA trial. Gut 1995; 37:509–511.
26. **Kelly JP, Kaufman DW, Jurgelon JM, Sheehan J, Koff RS, Shapiro S.** Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. Lancet 1996; 348:1413–1416.
27. **Cryer B, Kimmer MB.** Gastrointestinal side effects of nonsteroidal anti-inflammatory drugs. Am J Med 1998; 105:20S–30S.
28. **Robinson MG, Griffin JW Jr, Bowers J, et al.** Effect of ranitidine [on] gastroduodenal mucosal damage induced by nonsteroidal antiinflammatory drugs. Dig Dis Sci 1989; 34:424–428.
29. **Roth SH, Bennett RE, Mitchell CS, Hartman RJ.** Cimetidine therapy in nonsteroidal anti-inflammatory drug gastropathy. Double-blind long-term evaluation. Arch Intern Med 1987; 147:1798–1801.
30. **Agrawal NM, Roth S, Graham DY, et al.** Misoprostol compared with sucralfate in the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcer. A randomized, controlled trial. Ann Intern Med 1991; 115:195–200.
31. **Hudson N, Taha AS, Russell R, et al.** Famotidine for healing and maintenance in nonsteroidal anti-inflammatory drug-associated gastroduodenal ulceration. Gastroenterology 1997; 112:1817–1822.
32. **Taha AS, Hudson N, Hawkey CJ, et al.** Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal antiinflammatory drugs. N Engl J Med 1996; 334:1435–1439.
33. **Robinson M.** New-generation proton pump inhibitors: overcoming the limitations of early-generation agents. Eur J Gastroenterol Hepatol 2001; 13(suppl):S43–S47.
34. **Matheson AJ, Jarvis B.** Lansoprazole: an update of its place in the management of acid-related disorders. Drugs 2001; 61:1801–1833.
35. **Graham DY, Agrawal NM, Campbell DR, et al.** Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: results of a double-blind, randomized, multicenter, active- and placebo-controlled study of misoprostol vs. lansoprazole. Arch Intern Med 2002; 162:169-175.
36. **Sontag SJ, Kogut DG, Fleischmann R, et al.** Lansoprazole heals erosive reflux esophagitis resistant to histamine H_2-receptor antagonist therapy. Am J Gastroenterol 1997; 92:429–437.
37. **Hawkey CJ, Karrasch JA, Szczepañski L, et al.** Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management (OMNIUM) Study Group. N Engl J Med 1998; 338:727–734.

38. **Yeomans ND, Tulassay Z, Juhász L, et al.** A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment (ASTRONAUT) Study Group. N Engl J Med 1998; 338:719–726.
39. **Graham DY.** *Helicobacter pylori* and nonsteroidal anti-inflammatory drugs: interaction with proton pump inhibitor therapy for prevention of nonsteroidal anti-inflammatory drug ulcers and ulcer complications—future research needs. Am J Med 2001; 110:58S–61S.
40. **Graham DY, White RH, Moreland LW, et al.** Duodenal and gastric ulcer prevention with misoprostol in arthritis patients taking NSAIDs. Misoprostol Study Group. Ann Intern Med 1993; 119:257–262.
41. **Maetzel A, Ferraz MB, Bombardier C.** The cost-effectiveness of misoprostol in preventing serious gastrointestinal events associated with the use of nonsteroidal antiinflammatory drugs. Arthritis Rheum 1998; 41:16–25.
42. **Levine JS.** Misoprostol and nonsteroidal anti-inflammatory drugs: a tale of effects, outcomes, and costs. Ann Intern Med 1995; 123:309–310.
43. **Leandro G, Pilotto A, Franceschi M, Bertin T, Lichino E, DiMario F.** Prevention of acute NSAID-related gastroduodenal damage: a meta-analysis of controlled clinical trials. Dig Dis Sci 2001; 46:1924–1936.
44. **Graham DY.** Nonsteroidal anti-inflammatory drugs, *Helicobacter pylori*, and ulcers: where we stand. Am J Gastroenterol 1996; 91:2080–2086.
45. **Taha AS, Dahill S, Morran C, et al.** Neutrophils, *Helicobacter pylori*, and nonsteroidal anti-inflammatory drug ulcers. Gastroenterology 1999; 116:254–258.
46. **Aalykke C, Lauritsen JM, Hallas J, Reinholdt S, Krogfelt K, Lauritsen K.** *Helicobacter pylori* and risk of ulcer bleeding among users of nonsteroidal anti-inflammatory drugs: a case-control study. Gastroenterology 1999; 116:1305–1309.
47. **Bombardier C, Laine L, Reicin A, et al.** Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000; 343:1520–1528.
48. **Cullen DJ, Hawkey GM, Greenwood DC, et al.** Peptic ulcer bleeding in the elderly: relative roles of *Helicobacter pylori* and non-steroidal anti-inflammatory drugs. Gut 1997; 41:459–462.
49. **Huang JQ.** *H. pylori*, NSAID use, and risk of peptic ulcer disease: meta-analysis of 5 case control studies. Am J Gastroenterol 2000; 95:A146.
50. **Chan FKL, Chung SCS, Suen BY, et al.** Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. N Engl J Med 2001; 344:967–973.
51. **Watson DJ, Harper SE, Zhao PL, Quan H, Bolognese JA, Simon TJ.** Gastrointestinal tolerability of the selective cyclooxygenase-2 (COX-2) inhibitor rofecoxib compared with nonselective COX-1 and COX-2 inhibitors in osteoarthritis. Arch Intern Med 2000; 160:2998–3003.
52. **Laine L, Harper S, Simon T, et al.** A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2–specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. Rofecoxib Osteoarthritis Endoscopy Study Group. Gastroenterology 1999; 117:776–783.
53. **Simon LS, Weaver AL, Graham DY, et al.** Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis. A randomized controlled trial. JAMA 1999; 282:1921–1928.
54. **Emery P, Zeidler H, Kvien TK, et al.** Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. Lancet 1999; 354:2106–2111.
55. **Harper S, Bolognese J, Lee M, Watson DJ, Curtis S.** Fewer GI-related treatment discontinuations with etoricoxib compared with nonselective cyclooxygenase inhibitors (NSAIDs). In: Abstracts of The American College of Rheumatology 64th Annual Scientific Meeting; October 29-November 2, 2000; Philadelphia, PA. Abstract 1588.
56. **Harper S, Lee M, Curtis S, Ng J, Watson DJ, Bolognese J.** A lower incidence of upper-GI perforations, ulcers and bleeds (PUBs) in patients treated with etoricoxib vs. nonselective cyclooxygenase inhibitors (NSAIDs). In: Abstracts of The American College of Rheumatology 64th Annual Scientific Meeting; October 29-November 2, 2000; Philadelphia, PA. Abstract 1590.