

The Impact of Nonsteroidal Anti-inflammatory Drug-Induced Gastropathy

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Presentation Summary

Gastric and duodenal injury related to nonsteroidal anti-inflammatory drug (NSAID) use is extremely common, and a variety of strategies can be employed to reduce this frequent side effect of an otherwise useful category of medications. Although the best approach may be to discontinue NSAID treatment, this is not always possible for patients with arthritis pain or for those who require low-dose aspirin therapy for underlying cardiovascular disease. In arthritis cases, one of the new cyclooxygenase-2 specific inhibitors can be used to replace a traditional NSAID, but the addition of another drug to treat and heal ulcers is normally still needed. Patients taking aspirin are also candidates for additional treatment.

Approximately 100 million prescriptions for nonsteroidal anti-inflammatory drugs (NSAIDs) are given annually, and it is estimated that half of physicians' office visits for osteoarthritis or rheumatoid arthritis result in an NSAID prescription. In the United States, there are about 14 million daily NSAID users. Although NSAIDs provide excellent pain control for arthritis patients, 20% to 40% of NSAID users will have asymptomatic but endoscopically evident gastroduodenal damage. Erosive damage is most common and 25% of those taking NSAIDs will have evidence of an ulcer.

Clear data indicate that NSAID use is a leading cause of erosive gastric disorders, and preventive management should be considered for patients who must take these drugs.^{1,2}

Impact of NSAIDs

NSAID-related gastropathy is associated with considerable cost. According to one estimate, 69% of the total cost of arthritis treatment is used for actual treatment and 31% is used to treat the adverse gastrointestinal (GI) effects resulting from NSAID use. NSAID use is responsible for 15% to 60% of hospital admissions for GI bleeding, amounting to approximately 100,000 hospitalizations annually. If variceal bleeding cases are excluded, the majority of hospitalizations involve patients taking either aspirin or another NSAID. Also, effects associated with GI bleeding resulting from NSAID use cause between 10,000 and 20,000 deaths per year.³

The greatest predictor of NSAID toxicity and related bleeding is a history of ulcer or GI complications. Other risk factors include high-dose or multiple NSAID use, concomitant anticoagulant or corticosteroid use, advanced age, and coexisting major illness such as heart disease. It should be noted that cardiovascular disease is a risk factor independent of whether the patient is taking aspirin.⁴

The risk of aspirin-related GI complications is dose dependent. Two large case-controlled studies have shown that aspirin use is consistently associated with GI complications. Taking 75 mg of aspirin daily increases the risk by an odds ratio of 2.3; a 150-mg daily dose increases the risk ratio to 3.2; and a 300-mg daily dose increases the odds ratio to 3.9. Using buffered or enteric-coated aspirin does not reduce the risk of complications.^{5,6}

Dyspepsia. One of the most important NSAID-related side effects in terms of quality of life for both patients and physicians is dyspepsia. Dyspepsia is extremely common; some studies suggest that it occurs in up to half of NSAID users and is responsible for NSAID discontinuation in up to 25% of patients.⁷ The costs of diagnosis and management of NSAID-related dyspepsia, including additional prescriptions and diagnostic endoscopy, are estimated to be substantial.⁸ Unfortunately, dyspepsia related to NSAIDs is difficult to study and poorly characterized. Furthermore, it appears to be poorly correlated with endoscopic confirmation of damage to the gastric mucosa, and the relationship of dyspepsia to subsequent clinically important GI outcomes is uncertain.³

Mechanisms. The mechanism of NSAID-related GI toxicity is linked to cyclooxygenase-1 (COX-1) inhibition in the stomach, interference with prostaglandin-mediated protective factors, and impairment of blood flow in the microvasculature. In combination with NSAID-induced superficial damage to the epithelium, erosions and ulcers may form. The stomach and proximal duodenum are exposed to acid, which causes secondary damage (**Figure**).³ The mechanism of dyspepsia resulting from NSAID use is not clear. Researchers speculate that reflux may be a potential mechanism

for dyspepsia and other NSAID side effects, but more study is needed in this area.

Management Strategies

Endoscopic diagnosis should not be a first-line choice in NSAID users with GI symptoms and should be advocated only for patients with severe pain or with pain that is unresponsive to therapy, or for those with evidence of obstruction or occult or overt bleeding.

Several management strategies are possible with the most obvious being NSAID discontinuation. However, recurrence of arthritis pain makes this an unrealistic option for many patients. Lowering the NSAID dose may help some patients, and recommending that NSAIDs be taken with food or an antacid may reduce symptoms but not gastric or duodenal damage. Testing for and elimination of *Helicobacter pylori* may be helpful in many cases and is considered standard care when an ulcer is found.

Prophylactic therapy with misoprostol for NSAID-induced ulcers is problematic. This well-studied drug prevents gastric and duodenal ulcers and reduces ulcer complications by about 40%. However, misoprostol may cause abdominal pain and diarrhea and does not prevent dyspepsia. In addition, women of childbearing potential cannot take this drug. Tolerability is increased with lower doses of 200 mg twice daily, but decreased efficacy is seen at lower doses.⁹⁻¹¹

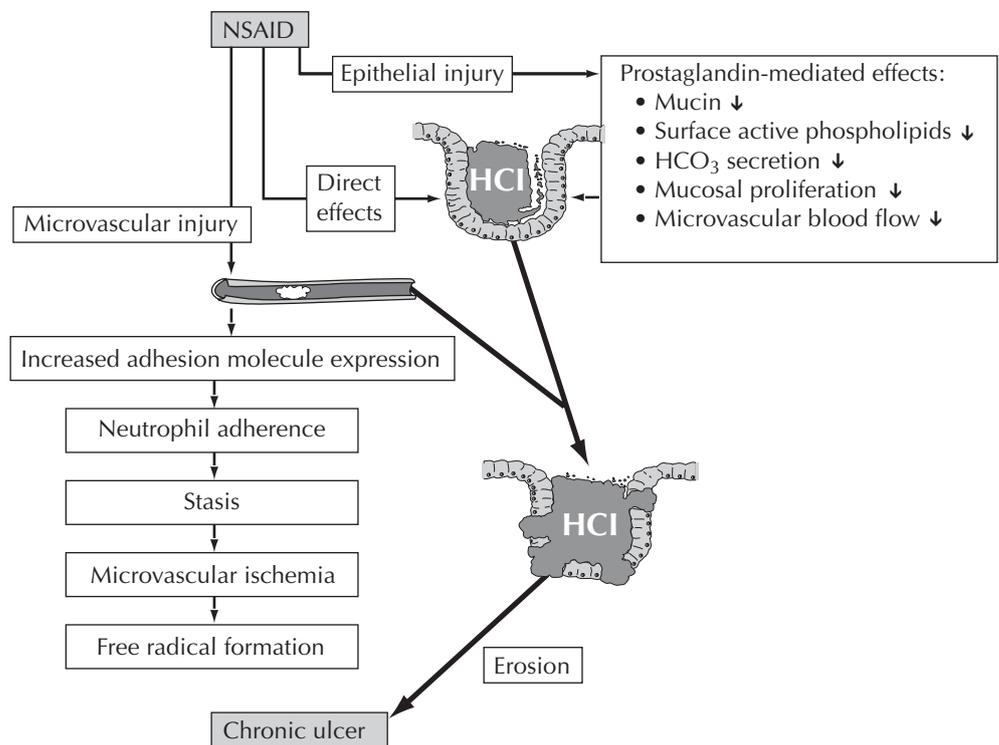
Histamine₂ Receptor Antagonists. Histamine₂ receptor antagonists (H₂RAs) are very effective in reducing dyspeptic symptoms and in treating and healing active ulcers, but they are most effective when NSAID use is discontinued, which is a significant limitation in treating many patients. H₂RAs only prevent gastric ulcers at very high doses. Although there are no long-term outcomes data on the

use of these agents, 1 study has suggested that ulcer complications continue to develop in patients taking a low-dose H₂RA, although the patients remain asymptomatic.¹²

Proton Pump Inhibitors. Two recent studies evaluated the effectiveness of the proton pump inhibitor (PPI) omeprazole. In the first study, 210 patients received 20 mg of omeprazole daily and 215 received 150 mg of the H₂RA ranitidine twice daily for 6 months in a secondary prevention trial. All patients had previous gastric ulcers that had healed or at least 10 gastric or duodenal erosions. Omeprazole maintained remis-

sion significantly longer than did ranitidine. Gastric ulcer recurrence rates during the study period were 16.3% for ranitidine and 4.5% for omeprazole. Duodenal ulcer recurrence rates were 3% for ranitidine patients and 0.25% for those taking omeprazole. The same study also examined the impact of omeprazole compared with ranitidine for ulcer healing in the face of continued NSAID use. After the first 8 weeks of treatment, 64% of NSAID-related gastric ulcers were healed with ranitidine treatment compared with 84% of those treated with omeprazole. Eighty-one percent of NSAID-related gastric ulcers were healed after 8

Figure. COX-1 Inhibition and GI Toxicity



COX-1 = cyclooxygenase-1; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; HCl = hydrochloric acid ; HCO₃ = bicarbonate.

Source: Adapted from Reference 3.

weeks with ranitidine compared with 92% with omeprazole.¹³

In the portion of the second study that evaluated patients for 6 months following ulcer healing who continued NSAID therapy, 20 mg of omeprazole daily was compared in 274 patients with 200 mg of the prostaglandin analogue misoprostol twice daily in 296 patients and placebo in 155 patients. Combined gastric and duodenal ulcer recurrence rates were 42% for placebo, 18% for misoprostol, and 14% for omeprazole. Omeprazole significantly reduced duodenal ulcer recurrence when compared with misoprostol. Researchers also noted an increased quality of life for omeprazole patients and a decreased quality of life for misoprostol patients.¹⁴

The advantages of PPI therapy for prophylactic treatment in NSAID users are that PPIs reduce dyspeptic symptoms and can treat and heal both gastric and duodenal ulcer disease. The main limitation is the lack of prospective outcome data for PPI therapy in this patient population; more long-term study is needed.

COX-2 Inhibition

Selective COX-2 inhibitors may be used to replace traditional NSAIDs in arthritis patients in an effort to reduce GI complications. Outcome and endoscopic data from 2 recent large studies show that these drugs reduce the incidence of upper GI bleeding and of complicated and symptomatic ulcers.^{15,16} In the study using rofecoxib, however, patients taking aspirin for underlying cardiovascular disease who discontinued aspirin therapy experienced higher myocardial infarction rates compared with those taking naproxen, indicating the importance of continuing low-dose aspirin therapy in these patients.¹⁵

In a study of celecoxib in arthritis patients, complicated ulcer incidence was reduced 62% and nuisance GI symptoms were reduced 30% com-

pared with traditional NSAIDs. However, in patients continuing aspirin therapy for cardiovascular prophylaxis, complicated ulcer incidence was reduced by only 47%. Overall, GI symptoms can still occur in patients taking COX-2 inhibitors; in fact, these drugs only reduce GI complications and symptoms by slightly less than one third compared with traditional pain-relieving agents.¹⁵

If an ulcer is present, a COX-2 inhibitor will probably continue to produce slow ulcer healing similar to that produced by NSAIDs. Therefore, the addition of a PPI once daily to the regimen will be helpful. If the patient can discontinue treatment with COX-2 inhibitors, NSAIDs, and aspirin, the addition of a PPI may not be necessary.

Conclusion

Chronic use of aspirin and NSAIDs carries a high risk of GI toxicity and injury. Although discontinuation of these drugs is the best management strategy, it may not be possible in patients requiring pain relief or preventive cardiovascular measures. Prophylactic therapy with a PPI is recommended for patients who continue to take NSAIDs and can reduce symptoms and heal gastric and duodenal ulcers. Replacing traditional NSAIDs with a COX-2 inhibitor in arthritis and other pain patients can reduce the risk of GI toxicity. However, a PPI should be added to the COX-2 inhibitor in those who already have an ulcer.

... REFERENCES ...

1. **Hernandez-Diaz S, Rodriguez LA.** Association between nonsteroidal anti-inflammatory drugs and GI tract bleeding/perforation: An overview of epidemiologic studies published in the 1990s. *Arch Intern Med* 2000;160:2093-2099.
2. **Wolfe MM, Lichtenstein DR, Singh G.** Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1999;340:1888-1899.

3. **Scheiman JM.** NSAIDs, gastrointestinal injury, and cytoprotection. *Gastroenterol Clin North Am* 1996;25:279-298.
4. **Griffin MR, Scheiman JM.** Prospects for the changing burden of toxicity due to NSAIDs. *Am J Med* 2001. In press.
5. **Kelly JP, Kaufman DW, Jurgelon JM, Sheehan J, Koff RS, Shapiro S.** Risk of aspirin-associated major upper GI bleeding with enteric-coated or buffered product. *Lancet* 1996;348:1413-1416.
6. **Weil J, Colin-Jones D, Langman M, et al.** Prophylactic aspirin and risk of peptic ulcer bleeding. *BMJ* 1995;310:827-830.
7. **Ofman JJ, Maclean C, Morton S, Straus W, Shekelle P.** The risk of dyspepsia and serious gastrointestinal complications from NSAIDs: A meta-analysis. *Gastroenterology* 1999; 116:A270.
8. **Griffin MR.** Epidemiology of nonsteroidal anti-inflammatory drug-induced gastric injury. *Am J Med* 1998;104:23S-29S.
9. **Graham DY, Agrawal NM, Roth SH.** Preventing NSAID-induced gastric ulcer with misoprostol: A multicenter, double-blind, placebo-controlled trial. *Lancet* 1988;2:1277-1280.
10. **Silverstein FE, Graham DY, Senior JR, et al.** Misoprostol reduces serious gastrointestinal complaints in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs: A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1996; 123:241-249.
11. **Raskin JB, White RH, Jackson JE, et al.** Misoprostol dosage in the prevention of non-steroidal anti-inflammatory drug-induced gastric and duodenal ulcers: a comparison of three regimens. *Ann Intern Med* 1995;123:344-350.
12. **Singh G, Triadafilopoulos G.** Epidemiology of NSAID-induced gastrointestinal complications. *J Rheumatol* 1999;56:18-24.
13. **Yeomans ND, Tulassay Z, Jukasy L, et al.** A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal anti-inflammatory drugs. Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-associated Ulcer Treatment (ASTRONAUT) Study Group. *N Engl J Med* 1998;338:719-726.
14. **Hawkey CJ, Karrasch JA, Szczepanski L, et al.** Omeprazole compared with misoprostol for ulcers associated with nonsteroidal anti-inflammatory drugs. Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNI-UM) Study Group. *N Engl J Med* 1998; 338:727-734.
15. **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; 343:1505-1584.
16. **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.