NSAIDs (including aspirin): Secondary prevention of gastroduodenal toxicity

AUTHOR: Mark Feldman, MD, MACP, AGAF, FACG
SECTION EDITOR: J Thomas Lamont, MD
DEPUTY EDITOR: Shilpa Grover, MD, MPH, AGAF

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INTRODUCTION

Nonselective (ie, inhibiting both cyclooxygenase [COX]-1 and COX-2) nonsteroidal anti-inflammatory drugs (NSAIDs), including low-dose aspirin, can cause considerable morbidity and mortality related to gastric and duodenal ulcer disease, particularly gastrointestinal (GI) bleeding [1].

The prevention of recurrent gastroduodenal toxicity associated with NSAID, low-dose aspirin, or both therapies (secondary prevention) will be reviewed here. Primary prevention and treatment of NSAID-related and/or low-dose aspirin-related gastroduodenal toxicity are discussed separately, as is the pathogenesis of the gastroduodenal toxicity. (See "NSAIDs (including aspirin): Primary prevention of gastroduodenal toxicity" and "NSAIDs (including aspirin): Treatment and secondary prevention of gastroduodenal toxicity" and "NSAIDs (including aspirin): Pathogenesis and risk factors for gastroduodenal toxicity".)

SECONDARY PREVENTION OF GASTRODUODENAL TOXICITY

Prevention of recurrent ulcer disease becomes critically important in patients with a history of gastroduodenal toxicity from nonsteroidal anti-inflammatory drugs (NSAIDs), low-dose aspirin or both therapies, and who require continued therapy. Only randomized secondary prevention

trials using clinical ulcer disease as the outcome (rather than an endoscopic outcome) are discussed below.

With continued NSAID therapy — There are occasional patients who must resume or continue NSAID therapy despite prior symptomatic gastroduodenal ulcers or erosions. In such high risk individuals, a proton pump inhibitor (PPI) is recommended for as long as the NSAID is used. In one trial of patients with bleeding ulcers who tested positive for *H. pylori* and had to remain on naproxen or low-dose aspirin, maintenance therapy with omeprazole was more effective in preventing recurrent upper gastrointestinal (GI) bleeding than anti-*H. pylori* therapy alone [2]. In clinical practice, however, ulcer patients who are *H. pylori* positive are generally treated with a PPI along with *H. pylori* eradication. (See "Peptic ulcer disease: Treatment and secondary prevention", section on 'Eradication of Helicobacter pylori (H. pylori)'.)

When first introduced, COX-2 inhibitors held promise as an alternative to traditional NSAIDs in preventing recurrent peptic ulcer disease in individuals who required ongoing anti-inflammatory therapy. Simply substituting a COX-2 inhibitor for the prior nonselective NSAID in patients with NSAID-related ulcer disease and ulcer complications should not be chosen over PPI maintenance therapy. This was demonstrated in a trial of 273 arthritis patients with NSAID-related bleeding ulcers. Once the ulcers had healed, the authors found that substituting celecoxib 200 mg bid plus esomeprazole (20 mg bid) for a year was significantly more effective in preventing recurrent bleeding ulcers than simply substituting celecoxib (plus placebo bid) for the NSAID that the patient had been taking previously [3]. Ulcer rebleeding rates after a median follow-up period of 13 months were 0 percent in the celecoxib/esomeprazole group and 8.9 percent in the celecoxib/placebo group (P=0.004).

With continued low-dose aspirin therapy — Low-dose aspirin (75 to 325 mg/day) is of proven benefit in the secondary prevention and, in selected patients, the primary prevention of cardiovascular disease [4]. However, patients treated with low-dose aspirin have an increased risk of gastrointestinal bleeding, which must be weighed against a possible decrease in cardiovascular mortality [5]. The risk of recurrent bleeding in aspirin users may be higher in patients without a past or current *H. pylori* infection [6]. (See 'Risk of stopping low-dose aspirin' below.)

Randomized trials support the efficacy of proton pump inhibitor (PPI) therapy in preventing recurrent bleeding in both *H. pylori* positive and negative patients receiving low-dose aspirin therapy. Different approaches using a PPI to prevent recurrent GI bleeding in patients who continue low-dose aspirin therapy have been evaluated in several randomized trials performed in East Asia [2,7-12].

Placebo-controlled trials showed a significant reduction in recurrent ulcer complications with PPI therapy among low-dose aspirin users. The trials can be summarized as follows:

- Among patients infected with *H. pylori*, the rate of recurrent ulcer complications was significantly lower at one year with lansoprazole (30 mg daily) compared to placebo (1.6 versus 14.8 percent). Lansoprazole or placebo was started after the ulcer had healed and *H. pylori* had been eradicated [7].

- A similar difference in recurrent bleeding at one year (0.7 versus 8.6 percent) in *H. pylori* negative patients was noted with esomeprazole (20 mg twice daily) plus low-dose aspirin (80 mg daily) compared to an esomeprazole placebo twice daily plus clopidogrel (75 mg/day) [8]. A similar trial was stopped early because of a higher bleeding rate in the clopidogrel group [9].

- Other trials in low-dose aspirin users compared different therapies without a placebo group. In one, a PPI (pantoprazole) was associated with a significantly lower rate of recurrent symptomatic or bleeding ulcers/erosions than an H2-blocker (famotidine) (0 versus 20 percent at 48 weeks) [10]. In a second trial, limited to patients who were *H. pylori* positive, there was no significant difference in recurrent bleeding at six months with omeprazole (20 mg/day) compared to anti-*H. pylori* therapy (0.9 versus 1.9 percent) [2]. In a third trial, rabeprazole (5 or 10 mg per day) markedly reduced the incidence of recurrent ulcers over 24 weeks compared to the comparator therapy, teprenone (a mucosal protective agent), with no bleeding ulcers occurring in the rabeprazole groups but in nearly 5 percent of the teprenone group [12].

In summary, patients who require low-dose aspirin for cardiovascular prophylaxis and have had a bleeding ulcer while taking low-dose aspirin should be treated with a PPI (rather than an H2-blocker), along with *H. pylori* eradication if they test positive for *H. pylori*. (See "Peptic ulcer disease: Treatment and secondary prevention", section on 'Eradication of Helicobacter pylori (H. pylori)'.)

There are no compelling data that suggest that any of the available PPIs are more effective than another. The table lists the available medications and their usual dose (table 1).

With continued NSAID and low-dose aspirin therapy — Some patients have multiple risk factors for gastroduodenal toxicity, including use of an NSAID and low-dose aspirin, and many of these patients are also at increased risk due their elderly status. (See "NSAIDs (including aspirin): Primary prevention of gastroduodenal toxicity".) Patients with a history of a complicated, NSAID-related peptic ulcer (especially if recent) who must resume an NSAID in addition to low-dose aspirin are at very high GI risk. A major controlled clinical trial was

performed in Hong Kong in patients with bleeding gastroduodenal ulcers related to NSAID and low-dose aspirin use. Once the ulcer had healed, patients were placed on celecoxib (COX-2 selective) plus esomeprazole or naproxen (COX nonselective) plus esomeprazole; both groups were encouraged to continue taking their low-dose aspirin. Although recurrent ulcer bleeding over the ensuing 18 months was common in both groups, it was significantly less common in the celecoxib group than in the naproxen group [13].

In another major clinical trial, 24,081 patients whose arthritis pain could not be controlled with acetaminophen were randomly assigned to receive either celecoxib, naproxen, or ibuprofen. Nearly half of them were also receiving low-dose aspirin for cardiovascular prophylaxis. All patients received esomeprazole co-therapy. Patients at very high GI risk due to recent ulcer complications or uncomplicated peptic ulcer disease were excluded, although some patients with a more remote history of ulcer disease may have been included. Thus, this study mainly compared celecoxib plus PPI with a nonselective NSAID plus PPI for primary prevention of GI toxicity, but in some patients, the study likely constituted a secondary prevention trial. Clinically significant GI events were uncommon during a median follow-up period of 34 months and were similar in the groups (celecoxib 0.7 percent, naproxen 0.7 percent, and ibuprofen 0.9 percent) [14].

In summary, if an NSAID and low-dose aspirin must be resumed in high GI risk patients, celecoxib plus a PPI may be preferred over naproxen plus a PPI. However, in patients at lower GI risk, celecoxib plus a PPI may not have an advantage over nonselective NSAIDs plus a PPI.

Risk of stopping low-dose aspirin — Benefits and risks of stopping low-dose aspirin were addressed in a randomized trial of 156 adults with cardiovascular or cerebrovascular disease who were being treated with low-dose aspirin and developed peptic ulcer bleeding. After control of bleeding with endoscopic therapy and use of a PPI, patients were assigned to continue taking aspirin (80 mg per day) or to stop the aspirin and switch to a placebo for eight weeks. Stopping aspirin therapy was associated with a nonsignificant decrease in the primary endpoint of recurrent ulcer bleeding within 30 days (5.4 percent versus 10.3 percent with continued aspirin therapy). Stopping aspirin was also associated with a significant increase in the secondary endpoint of overall mortality at eight weeks (12.3 versus 1.3 percent) [15]. Because the magnitude of this mortality difference was much greater than seen in previous large randomized trials of secondary prevention of cardiovascular disease with much longer follow-up, the authors appropriately concluded that larger trials are needed to confirm their findings. (See "Aspirin for the secondary prevention of atherosclerotic cardiovascular disease", section on 'Efficacy'.)

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".)

SUMMARY AND RECOMMENDATIONS

- For patients with symptomatic gastroduodenal ulcers or numerous erosions who must continue nonsteroidal anti-inflammatory drug (NSAID), low-dose aspirin therapy or both, we recommend treatment with a proton pump inhibitor for as long as the NSAID and/or aspirin is used (table 1) (**Grade 1A**). (See 'Secondary prevention of gastroduodenal toxicity' above.)

- In addition, we recommend that *H. pylori* infection be eradicated, if known to be present (**Grade 1A**). (See "Peptic ulcer disease: Treatment and secondary prevention", section on 'Eradication of Helicobacter pylori (H. pylori)' and "Treatment regimens for Helicobacter pylori in adults".)

- Selecting celecoxib (or perhaps another COX-2 selective agent, if available) plus a proton pump inhibitor for patients who are at very high gastrointestinal (GI) risk and who are taking low-dose aspirin for cardiovascular prophylaxis may be more effective than using a nonselective NSAID plus a proton pump inhibitor in reducing recurrent bleeding ulcers. Nevertheless, recurrent GI bleeding remains a concern in such patients. (See 'With continued NSAID therapy' above.)

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GRAPHICS

Recommendations for PPI doses in active therapy of uncomplicated gastroduodenal ulcers*

Drug	Dose (adult)
Dexlansoprazole	30 to 60 mg
Esomeprazole	20 to 40 mg
Lansoprazole	30 mg
Omeprazole	20 to 40 mg
Pantoprazole	40 mg
Rabeprazole	20 mg
All administered by mouth daily before breakfast	

PPI: proton pump inhibitor.

* As a general rule, active duodenal ulcers should be treated for four to six weeks and gastric ulcers for six to eight weeks.

Adapted from: Wolfe MM, Sachs G. Acid suppression: Optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology 2000; 118:S9.

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