Similar Rate of Ulcer Recurrence with Naproxen plus Lansoprazole versus Celecoxib

Lai KC, Chu KM, Hui WM, et al. Celecoxib compared with lansoprazole and naproxen to prevent gastrointestinal ulcer complications. Am J Med 2005;118:1271–8.

Study Overview

Objective. To compare the rate of recurrent gastrointestinal (GI) ulceration with selective cyclooxygenase-2 (COX-2) inhibitor therapy versus combination therapy with a nonselective nonsteroidal anti-inflammatory drug (NSAID) and a proton pump inhibitor (PPI) in individuals with a history of NSAID-related peptic ulcers.

Design. Prospective, open-label, randomized controlled trial.

Setting and participants. Participants at a single academic medical center in Hong Kong were identified from patients who had been admitted with upper GI bleeding while taking NSAIDs. Patients were included if they were older than 18 years, had a gastric or duodenal ulcer ≥ 5 mm in diameter on endoscopy, and had a concomitant diagnosis requiring chronic NSAID use (eg, rheumatoid arthritis, osteoarthritis). Patients were excluded if they had any history of gastric or duodenal surgery; were allergic to the study drugs; had uncontrolled hypertension, active malignancy, congestive heart failure, or chronic renal insufficiency; or used aspirin or anticoagulants.

Intervention. Participants were randomized to either 200 mg celecoxib (a selective COX-2 inhibitor) once daily or combination therapy with 250 mg naproxen (a nonselective NSAID) 3 times daily and 30 mg lansoprazole (a PPI) once daily. Study duration was 24 weeks. Prior to randomization, all patients were tested for *Helicobacter pylori* infection and subsequently treated, if indicated. Patients with *H. pylori* infections who failed initial therapy were re-treated. Patients who did not have *H. pylori* infections were treated with twice-daily famotidine (20 mg) for 6 weeks and were given an additional 8 weeks of therapy if they had persistent unhealed ulcers. Any patient with either persistent *H. pylori* infection or unhealed ulcers were excluded from the study. Randomization occurred after treatment for the presenting GI ulcer was complete.

Main outcome measures. The primary study outcome was recurrent gastric or duodenal ulcer complication. Secondary outcome measures included overall adverse events and efficacy of treatment for arthritis pain. Endoscopy was performed in patients with symptoms of ulcer relapse, dyspepsia not responding to antacid treatment, a decrease in hemoglobin level of ≥ 2 g/dL, or a positive fecal occult blood test.

Main results. Of 242 patients, 120 patients were allocated to celecoxib therapy and 122 were allocated to naproxen plus lansoprazole. Baseline characteristics were similar between the 2 groups. Four patients had recurrent ulcer complications in the celecoxib group as compared with 7 patients in the naproxen/lansoprazole group. There was no statistically significant difference in the cumulative incidence of recurrent GI ulcers between the celecoxib group (3.7% [95% confidence interval {CI}, 0.0%–7.3%) and the naproxen/lansoprazole group (6.3% [95% CI, 1.6%–11.1%). The incidence of dyspepsia was higher in the celecoxib group as compared with the naproxen/lansoprazole group (15% versus 5.7%; $P = 0.02$). The rates of other side effects, such as peripheral edema, hypertension, and elevated creatinine level, were similar between the 2 groups as was control of arthritis pain.

Conclusion. Combination therapy with naproxen and lansoprazole resulted in a similar rate of GI ulcer recurrence and complications compared with celecoxib monotherapy. However, more patients in the celecoxib group experienced dyspepsia. Both therapies had similar efficacy in controlling arthritis pain.

Commentary

NSAID use is a strong risk factor for GI ulceration [1], and this risk is particularly relevant for patients on chronic NSAIDs for arthritic pain. Because this toxicity is associated with significant morbidity and mortality [2], the development of selective COX-2 inhibitors was met with great enthusiasm. Although COX-2 inhibitors are less likely to result in GI ulceration than nonselective NSAIDs [3], recent revelations about cardiovascular toxicities of COX-2 inhibitors has caused providers to re-evaluate how these medications should fit into their treatment algorithms [4,5]. This study by Lai et al demonstrates that it might be possible to

achieve the same GI protective effect of the COX-2 inhibitors using nonselective NSAIDs combined with PPIs.

Although Lai et al's results might provide reassurance to providers looking for ways to control arthritis symptoms in patients at high risk for GI ulceration, several caveats must be noted. First, the study duration was relatively short. The Kaplan-Meier curves comparing GI ulceration and complications between the 2 groups started to show a greater separation after week 18, favoring the celecoxib group. Whether this divergence would have reached a statistically significant result after 24 weeks (the median duration of the trial) is unknown. A second weakness of the study was that subjects on aspirin were excluded; providers would likely be most concerned about using celecoxib for GI protection in patients with cardiovascular disease (who would likely be taking aspirin). Thus, the results of the study may not be generalizable to this group of patients, a population that providers might need the most guidance on regarding chronic anti-inflammatory therapy. Additional research will be needed to clarify how chronic aspirin use could impact the risk of recurrent NSAID-related ulceration in patients being treated with celecoxib or a combination of a nonselective NSAID and a PPI.

Applications for Clinical Practice

For patients with a past history of NSAID-related GI ulceration, combination therapy with naproxen and lansoprazole had a similar risk of recurrent ulceration as compared with celecoxib; however, this risk was high in both groups. In patients at increased risk for NSAID-related ulceration and with concomitant cardiovascular disease, providers may choose to prescribe a combination of a nonselective NSAID and a PPI rather than a COX-2 inhibitor for control of arthritic pain. Further research is necessary, however, to see how the addition of aspirin therapy impacts these ulcer prevention strategies.

–Review by Harvey J. Murff, MD, MPH

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