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CLINICAL RESEARCH STUDY

Celecoxib compared with lansoprazole and naproxen to prevent gastrointestinal ulcer complications

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ABSTRACT

PURPOSE: Selective cyclooxygenase-2 (COX-2) inhibitors cause significantly fewer peptic ulcers than conventional nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) in patients at low risk or high risk for peptic ulcers. On the other hand, proton pump inhibitor co-therapy has also been shown to be effective in preventing relapse of peptic ulcers in high-risk patients using nonselective NSAIDs. We compared the efficacy of a selective COX-2 inhibitor with that of proton pump inhibitor co-therapy in the reduction in the incidence of ulcer relapse in patients with a history of NSAID-related peptic ulcers.

MATERIALS AND METHODS: For this study, we recruited 224 patients who developed ulcer complications after NSAID use. We excluded patients who required concomitant aspirin treatment and who had renal impairment. After healing of ulcers and eradication of *Helicobacter pylori*, patients were randomly assigned to treatment with celecoxib 200 mg daily (n = 120) or naproxen 750 mg daily and lansoprazole 30 mg daily (n = 122) for 24 weeks. The primary endpoint was recurrent ulcer complications.

RESULTS: During a median follow-up of 24 weeks, 4 (3.7%, 95% confidence interval [CI] 0.0%-7.3%) patients in the celecoxib group, compared with 7 patients (6.3%, 95% CI 1.6%-11.1%) in the lansoprazole group, developed recurrent ulcer complications (absolute difference −2.6%; 95% CI for the difference −9.1%-3.7%). Celecoxib was statistically non-inferior to lansoprazole co-therapy in the prevention of recurrent ulcer complications. Concomitant illness (hazard ratio 4.72, 95% CI 1.24-18.18) and age 65 years or more (hazard ratio 18.52, 95% CI 2.26-142.86) were independent risk factors for ulcer recurrences. Significantly more patients receiving celecoxib (15.0%, 95% CI 9.7-22.5) developed dyspepsia than patients receiving lansoprazole (5.7%, 95% CI 2.8-11.4. $P = .02$).

CONCLUSIONS: Celecoxib was as effective as lansoprazole co-therapy in the prevention of recurrences of ulcer complications in subjects with a history of NSAID-related complicated peptic ulcers. However, celecoxib, similar to lansoprazole co-therapy, was still associated with a significant proportion of ulcer complication recurrences. In addition, more patients receiving celecoxib developed dyspepsia than patients receiving lansoprazole and naproxen.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used classes of drugs. However, chronic use of NSAIDs puts patients at risk for perforations, ulcers, or hemorrhage of the gastroduodenal mucosa.[1,2] Use of proton pump inhibitors reduces the incidence of relapse of both endoscopic ulcers and ulcer complications.[3,4] Recent studies suggest that the GI side effects of conventional NSAIDs are mediated through the inhibition of cyclooxygenase-1 (COX-1) enzyme. This is supported by studies showing that selective COX-2 inhibitors that spare the inhibition of COX-1 enzyme reduce the development and relapse of both endoscopical ulcers and GI complications in patients at low risk or high risk for peptic ulcers.[5,6]

In this study, we compared the efficacy of selective cyclooxygenase-2 (COX-2) inhibitors with that of proton pump inhibitor co-therapy in the prevention of ulcer relapse in patients with a history of NSAID-related ulcers. We hypothesized that selective COX-2 inhibitor was not inferior to proton pump inhibitor co-therapy in preventing ulcer relapse. Because low-dose aspirin alone is also associated with an increased risk of gastrointestinal (GI) bleeding[7] and may reduce the GI benefits of celecoxib,[8] we limited our study to patients who did not require concomitant aspirin treatment.

Methods

Study population

We screened patients, aged 18 years or older, who were admitted to the departments of medicine or surgery with upper GI bleeding while receiving NSAIDs. Endoscopy was performed within 24 hours after admission. Patients were recruited into the study if gastric and/or duodenal ulcer, defined as a break in the mucosa of at least 5 mm in diameter with unequivocal depth, was found on endoscopy and they had diseases (eg, osteoarthritis, rheumatoid arthritis) that were expected to require continuous treatment with an NSAID for the duration of the trial. Patients were excluded from study participation if they had history of gastric or duodenal surgery other than an oversew of a perforation, allergy to the study drugs or sulphonamides, uncontrolled hypertension; active malignancy; congestive heart failure, and concomitant anticoagulant and/or low-dose aspirin use. Patients were also excluded if they had any abnormal pretreatment creatinine levels, because both selective COX-2 inhibitors and nonselective NSAIDs could aggravate any preexisting renal impairment.[9]

Study protocol

This prospective open-labeled, randomized, controlled trial was conducted at the Queen Mary Hospital, University of Hong Kong, from November 1999 to May 2003. The ethics committee of the University of Hong Kong reviewed and approved the protocol. All patients gave written informed consent before participating in the study.

During endoscopy, 2 biopsy specimens were taken from the antrum. One specimen was subjected to a rapid urease test (CLO test, Delta West, Bently, Australia), and one specimen underwent microscopic examination for *Helicobacter pylori* using hematoxylin-eosin stain and Giemsa stain. *H. pylori* was considered to be present if either one of the 2 test results was positive; it was considered to be absent or successfully eradicated when both test results were negative. The microscopical detection of *H. pylori* is not affected by the continuous administration of a histamine H2 antagonist.[10]

Treatment and randomization

Eligible patients with *H. pylori* received a 1-week course of anti-*Helicobacter* therapy containing lansoprazole 30 mg, amoxicillin 1 g, and clarithromycin 500 mg twice daily, followed by famotidine 20 mg twice daily for 5 weeks (Figure 1). Patients without *H. pylori* infection received famotidine 20 mg twice daily for 6 weeks. Patients with endoscopically unhealed ulcers were given 20 mg of famotidine twice daily for another 8 weeks. Patients with failed *H. pylori* eradication received another 1-week course of antibiotic therapy. Patients with persistent unhealed ulcers and *H. pylori* infection were excluded from the study.

Eligible patients were randomly assigned to receive for 24 weeks either 200 mg of celecoxib, given once daily (celecoxib group), or 250 mg of naproxen, given 3 times daily, and 30 mg of lansoprazole, given once daily (lansoprazole group). Randomization was performed by drawing a sealed envelope that contained a predetermined random treatment generated by computer.

Follow-up and assessments

Patients returned for follow-up visits every 8 weeks after the initial dose of study medication. An antacid (Gelusil; Pfizer, New York, NY) was allowed for the control of symptoms of dyspepsia. Drug compliance was assessed by counting the number of tablets returned.

At each clinic visit, overall tolerability was assessed. These included adverse experiences, physical examinations, blood pressure, and laboratory measurements.

At all visits or when treatment was discontinued, the efficacy of treatment on controlling the arthritis activity was assessed by physicians' and patients' global assessment of arthritis using a 5-point scale (0 = very well, 1 = well, 2 = fair, 3 = poor, 4 = very poor) and by the patients' assessment of arthritis pain marked on a visual analogue scale from 0 mm (no pain) to 100 mm (severe pain).

In between visits, patients were asked to report to the study coordinator if they had persistent ulcer and GI symptoms (dyspepsia or recurrent vomiting) not relieved by antacids, or to the emergency department if they had evidence