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

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Background: Studies that report prevention of ulcer recurrence among long-term users of nonsteroidal anti-inflammatory drugs (NSAIDs) that do not stratify for Helicobacter pylori status may not be generalizable to the large population of individuals without H pylori.

Methods: This was a prospective, double-blind, multicenter, active- and placebo-controlled study among 537 patients without H pylori who were long-term users of NSAIDs and who had a history of endoscopically documented gastric ulcer. Patients were randomized to receive placebo, 200 µg of misoprostol 4 times a day, or 15 or 30 mg of lansoprazole once daily for 12 weeks. Ulcer status was determined by endoscopy at 4, 8, and 12 weeks.

Results: Patients receiving lansoprazole (15 or 30 mg) remained free from gastric ulcer longer than those who received placebo ($P < .001$) but for a shorter time than those who received misoprostol. By week 12, the percentages of gastric ulcer–free patients were as follows: placebo, 51% (95% confidence interval [CI], 41.1%-61.3%); misoprostol, 93% (95% CI, 87.2%-97.9%); 15-mg lansoprazole, 80% (95% CI, 72.5%-87.3%); and 30-mg lansoprazole, 82% (95% CI, 75.0%-89.6%). A significantly higher proportion of patients in the misoprostol group reported treatment-related adverse events and early withdrawal from the study. When the impact of withdrawals on ulcer development was considered (as failures), therapy was successful for 69% for each of the active treatment groups and 35% for the placebo group.

Conclusions: Proton pump inhibitors such as lansoprazole are superior to placebo for the prevention of NSAID-induced gastric ulcers but not superior to misoprostol, 800 µg/d. When the poor compliance and potential adverse effects associated with misoprostol are considered, proton pump inhibitors and full-dose misoprostol are clinically equivalent.

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ONSTEROIDAL anti-inflammatory drugs (NSAIDs) are widely used for the relief of pain and inflammation associated with arthritis and other musculoskeletal disorders. The benefit in terms of relief from pain and stiffness is accompanied by the risk of developing a peptic ulcer and a serious, life-threatening ulcer complication.1 Several studies2,3 have been performed in search of cotherapies that might prevent NSAID-induced ulcers and ulcer complications. The use of the synthetic prostaglandin, misoprostol (Cytotec; Pharmacia, Bridgewater, NJ), as a form of replacement therapy repeatedly has been shown to prevent NSAID-induced gastrointestinal ulcers and reduce the incidence of life-threatening ulcer complications.6-14 In contrast, neither the topical agent sucralfate nor usual doses of histamine2 (H2)-receptor antagonists have been shown to be effective.6,11,15-18 Increased doses of H2-receptor antagonists were more effective than lower doses, but overall, the success rate was modest.17,19-23

Recently, more profound acid suppression with proton pump inhibitors has been reported as being associated with acceleration of ulcer healing and prevention of ulcer relapse among long-term users of NSAIDs.10,18 Neither of the 2 large multicenter studies comparing the proton pump inhibitor omeprazole with misoprostol (Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management [OMNIUM])10 or ranitidine (Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment [ASTRONAUT])18 for the prevention of ulcer recurrence among long-term users of NSAIDs presented analyses regarding the association between Helicobacter pylori status and prevention of ulcer relapse. Subsequent analyses showed that H pylori status had a marked effect on outcome and the development of
PATIENTS AND METHODS

Entry criteria included being 18 years or older, history of endoscopically documented gastric ulcer with or without coexisting duodenal ulcer or gastrointestinal bleeding, and treatment with stable, full therapeutic doses of an NSAID (with the exception of nabumetone or aspirin ≥1300 mg/d; low-dose aspirin for cardiovascular protection was permitted) for at least the previous month. Two thirds of patients enrolled in this study had previously completed participation in a healing trial for NSAID-associated gastric ulcer. Pretreatment *H pylori* status was determined by a rapid urease test (CLOtest; Tri-Med Specialties Inc, Draper, Utah) or histologic analysis, which was graded according to the updated Sydney System.22 Those patients positive for *H pylori* were excluded, as were those with gastric or duodenal ulcer crater (≥5 mm in diameter) or severe erosions (defined as ≥25 erosions) or erosive reflux esophagitis. Use of a proton pump inhibitor, H2-receptor antagonist, or misoprostol within 24 hours before study entry was not permitted. Approval for the study was obtained from the institutional review board of each of the 63 participating centers in North America, and written informed consent was obtained before patient enrollment.

STUDY DESIGN

Patients were randomly assigned in blocks of 4 to receive 12 weeks of placebo, 200 µg of misoprostol 4 times daily with or after meals and a bedtime snack, or 15 or 30 mg of lansoprazole once daily before breakfast. Both patients and investigators remained masked to treatment group (with the exception of those receiving misoprostol). Patients received antacid tablets (Gelusil; Parke-Davis, Morris Plains, NJ) for use as needed for symptom relief. Patients were instructed to avoid antiulcer medication other than study medication, ulcerogenic medication (except NSAIDs or aspirin as noted herein), and agents that alter hemostasis. Compliance and adverse events were assessed by returned pill count and direct questioning at each treatment visit. Symptoms were assessed on a daily basis by patient diary, where patients recorded episodes of daytime and nighttime abdominal pain (defined as none, mild, moderate, or severe), study drug and NSAID dosing information, and frequency of antacid consumption. Endoscopy with biopsy was performed each month for 3 consecutive months to determine the presence of a gastric ulcer(s). Esophageal and duodenal mucosa were also evaluated.

STATISTICAL ANALYSIS

Statistical analyses were conducted using statistical software (SAS version 6.12; SAS Institute Inc, Cary, NC). Given a gastric ulcer prevention rate of 92% for one of the active treatment groups at the week 12 evaluation and a lower limit of 10%, a sample size of 120 subjects per treatment group would have 81% power to show noninferiority between active treatment groups.

Per-protocol and intent-to-treat analyses were conducted for ulcer occurrence, abdominal pain, and antacid use, the latter based on patient daily diary data. For all efficacy and safety end points, pairwise comparisons were made between treatment groups.

The comparability of the treatment groups at baseline was assessed with respect to demographic variables using the χ2 test (F test for age) and medical and social histories by the Fisher exact test. Baseline severity of symptoms, based on an investigator interview, was compared among the treatment groups using the Cochran-Mantel-Haenszel method for ordered response variables. Life table methods were used to estimate the ulcer incidence rates. The life table analysis of time to ulcer occurrence was performed using the Cochran-Mantel-Haenszel method to test treatment differences between groups. Factors including age; sex; race; treatment for an acute NSAID-associated gastric ulcer immediately before study enrollment; hiatal hernia; investigator, alcohol, tobacco, or caffeine use; and acute baseline gastric ulcer size (measured during a screening endoscopy conducted when the subject participated in a previous healing study) were controlled for in the analysis. The treatment groups were compared with respect to percentage of days with and average severity of daytime and nighttime abdominal pain and amount of antacid use based on diary data using the Wilcoxon 2-sample test. The Fisher exact test was used to compare the incidence of treatment-related adverse events (defined as possibly or probably related) between the treatment groups.

This study attempted to overcome some of the shortcomings of the OMNIUM and ASTRONAUT studies.10,18 Although the OMNIUM study evaluated 2 doses of the proton pump inhibitor for ulcer healing, this comparison was not extended to the ulcer prevention portion of the study, in which only the lower dose, 20 mg, was used.10 Those studies also used a dose of misoprostol essentially devoid of antisecretory activity and a dose of ranitidine that had been proven to be subtherapeutic for this indication (ie, 400 µg/d and 300 mg/d, respectively).11,12,15,16 In addition, they did not separate unequivocal NSAID ulcers from those complicated by *H pylori* infection. We report the results of a large, double-blind, multicenter, randomized, active- and placebo-controlled study designed to identify the optimal therapy for preventing unequivocal NSAID-induced gastric or duodenal ulcers. This study compared 2 doses of lansopra-

endoscopic ulcers, with *H pylori* infection being associated with an overrepresentation of duodenal ulcers,24 Separation of the prevention of ulcers that are unequivocally related to NSAID use and not to *H pylori* infection is important to the clinician because there are now considerable data to suggest the gastroduodenal outcome in long-term users of NSAIDs differs among those with and without *H pylori* infection.23,25 In addition, the presence of an ulcer in an *H pylori*–infected NSAID user is an indication for eradication of the infection because it is impossible to ascertain which was the actual cause of the ulcer. There is also increasing evidence that the use of antisecretory therapy with H2-receptor antagonists or proton pump inhibitors is associated with acceleration of corpus gastritis in those with *H pylori* infection,26-31 which may make it prudent to eradicate *H pylori* in those for whom long-term NSAID and antisecretory cotherapy is contemplated.
zole (Prevacid; TAP Pharmaceutical Products Inc, Lake Forest, Ill) (15 and 30 mg) with the full therapeutic dose of misoprostol (800 µg/d) and placebo for preventing ulcer relapse among patients who continued NSAID use and were known to be free of *H pylori*.

### RESULTS

A total of 537 patients were randomized to receive placebo (n=134), 200 µg of misoprostol 4 times a day (n=134), 15 mg of lansoprazole once daily (n=136), or 30 mg of lansoprazole once daily (n=133) for 12 weeks. Two patients (1 each in the placebo and 30-mg lansoprazole groups) who did not take study medication were not included in the intent-to-treat analysis of ulcer occurrence or adverse events (Table 1). Eighty-two (15%) of the 537 enrolled patients were excluded from the per-protocol analyses because of noncompliance (eg, fewer than 14 days and/or less than 67% of prescribed study medication taken during the treatment period; n=33), no evaluable endoscopy after the initiation of treatment (n=21), positive for *H pylori* at baseline (n=15), inappropriate ulcer history (n=6), and other reasons (n=10). (Three patients were excluded in 2 categories but were counted once in the total of 82 excluded patients.) The reasons for exclusion from the per-protocol analyses were generally balanced across the treatment groups with the exception that more patients in the misoprostol group did not take the minimum amount and/or complete the minimum duration necessary for evaluability (7, 19, 1, and 6 patients in the placebo, misoprostol, 15-mg lansoprazole, and 30-mg lansoprazole groups, respectively).

The treatment groups were well matched at baseline, including demographic characteristics, social history, previous history of gastrointestinal disorders, recent treatment for an NSAID-associated gastric ulcer, and severity of symptoms (Table 2). Most patients reported no daytime or nighttime abdominal pain at baseline. Forty percent of the patients used ibuprofen, 35% used naproxen, 32% used diclofenac, 22% used aspirin or aspirin combinations, 17% used piroxicam, and 34% used other NSAIDs. The distribution across treatment groups was similar. Patients could have taken more than 1 NSAID.

### Table 1. Patient Disposition by Treatment Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Misoprostol, 200 µg 4 Times Daily</th>
<th>Lansoprazole, 15 mg/d</th>
<th>Lansoprazole, 30 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>134</td>
<td>134</td>
<td>136</td>
<td>133</td>
</tr>
<tr>
<td>Randomized</td>
<td>134</td>
<td>134</td>
<td>136</td>
<td>133</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>23</td>
<td>23</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Did not receive study drug</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Adverse event</td>
<td>9</td>
<td>14</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Personal reasons</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Poor compliance</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Therapeutic failure</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Completed trial</td>
<td>111</td>
<td>111</td>
<td>122</td>
<td>114</td>
</tr>
</tbody>
</table>

Primary ulcer prevention data throughout the 12-week treatment period

ULCER PREVENTION

Evaluative patients taking an NSAID in the 15- and 30-mg lansoprazole groups remained free from gastric ulcer significantly longer than those who received placebo ($P<.001$). There was no difference between lansoprazole dosage groups ($P=.62$). Evaluative patients in the misoprostol group remained free of gastric ulcer significantly longer than those who received placebo ($P<.001$), 15-mg lansoprazole ($P=.01$), or 30-mg lansoprazole ($P=.04$). These observations were unaffected after adjustment for potentially influential factors, including age, sex, race, treatment for an acute NSAID-associated gastric ulcer before study enrollment, hiatal hernia, investigator, and alcohol, tobacco, or caffeine use. There were no statistically significant differences between any of the active treatment groups after adjusting for acute baseline gastric ulcer size. Similar trends were observed in the results of the intent-to-treat analysis of gastric ulcer prevention data throughout the 12-week treatment period.

Absence of a gastric ulcer after 8 or 12 weeks of treatment was different among those receiving placebo, misoprostol, or lansoprazole. By week 12, the percentages of evaluable patients who were free of gastric ulcer were 51% (95% confidence interval [CI], 41.1%-61.3%), 93% (95% CI, 87.2%-97.9%), 80% (95% CI, 72.5%-87.3%), and 82% (95% CI, 75.0%-89.6%) for the respective treatment groups (Figure 1). When prevention rates were analyzed based on the development of gastric or duodenal ulcers (gastrointestinal ulcers), those in the misoprostol, 15-mg lansoprazole, or 30-mg lansoprazole groups remained free of ulcer for a significantly longer period compared with those who received placebo ($P<.001$). There was no statistical difference between any 2 of the active treatments for time to occurrence of gastrointestinal ulcers (Figure 2).

To evaluate the impact of the early patient withdrawals from the misoprostol group, the worst-case scenario, where patients who withdrew from the study prematurely (eg, because of an adverse event) were classified as a treatment failure (eg, equivalent to having a gastric ulcer), was evaluated. In this scenario, the proportion of patients who were treatment successes
were identical for the misoprostol and lansoprazole groups and 2-fold higher than that for the placebo group (69% for each treatment group vs 35% for placebo). When those patients withdrawing prematurely were classified as the worse case (ie, having had a gastric or duodenal ulcer), the percentages of patients remaining free from gastroduodenal ulcer disease throughout the study period were 34%, 67%, 69%, and 68% for the placebo, misoprostol, 15-mg lansoprazole, and 30-mg lansoprazole groups, respectively.

**PATIENT DIARY RESULTS**

Lansoprazole-treated patients experienced significantly less severe and significantly fewer days with daytime abdominal pain than evaluable misoprostol-treated patients based on analyses of patient diaries (Table 3). Patients in the 15-mg lansoprazole group also had significantly less severe ($P = .01$) and significantly fewer days ($P = .001$) with nighttime abdominal pain than those in the misoprostol group. Antacid use was significantly
less (P<.001 for each pairwise comparison) among patients in the lansoprazole groups compared with patients in the misoprostol and placebo groups based on fewer antacid tablets taken per day and a smaller percentage of days of antacid use. Similar trends were observed in the results of the intent-to-treat analysis of diary data throughout the 12-week treatment period.

COMPILATION AND ADVERSE EFFECTS

More than 90% of patients in the placebo and 15- and 30-mg lansoprazole groups were compliant with study medication, compared with 73% of patients in the misoprostol group (P<.001). Thirty-eight (7%) of the 535 patients discontinued use of the study medication prematurely primarily because of an adverse event (9, 14, 4, and 10 patients in the placebo, misoprostol, 15-mg lansoprazole, and 30-mg lansoprazole groups, respectively).

A significantly higher percentage of patients in the misoprostol group (31%, 41/134) reported a treatment-related adverse event compared with each of the other treatment groups: 13 (10%) of 133 patients in the placebo group, 10 (7%) of 136 patients in the 15-mg lansoprazole group, and 21 (16%) of 132 patients in the 30-mg lansoprazole group (P<.001 for misoprostol vs placebo and vs 15-mg lansoprazole; P=.006 for misoprostol vs 30-mg lansoprazole; P=.04 for 15-mg lansoprazole vs 30-mg lansoprazole). The most commonly reported treatment-related event was diarrhea, which was more common in the misoprostol group (22%, 29/134) compared with the placebo (3%, 4/133), 15-mg lansoprazole (3%, 4/136), and 30-mg lansoprazole (7%, 9/132) groups (P=.001 for each comparison vs misoprostol). Patients in the misoprostol group also had a significantly greater incidence of treatment-related abdominal pain (6%, 8/134) and nausea (4%, 6/134) compared with patients in the 15-mg lansoprazole group (0/136 for both symptoms) (P=.003 and P=.01, respectively). One patient (in the 15-mg lansoprazole group) experienced an upper gastrointestinal tract hemorrhage during the study.

Table 3. Mean Diary Results During the 12-Week Treatment Period

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 113)</th>
<th>Misoprostol, 200 µg 4 Times Daily (n = 108)</th>
<th>Lansoprazole, 15 mg/d (n = 126)</th>
<th>Lansoprazole, 30 mg/d (n = 119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime abdominal pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days with pain, %</td>
<td>34.5</td>
<td>41.0</td>
<td>27.5†</td>
<td>30.8§</td>
</tr>
<tr>
<td>Average pain severity per day*</td>
<td>0.51</td>
<td>0.60</td>
<td>0.39‡</td>
<td>0.46§</td>
</tr>
<tr>
<td>Nighttime abdominal pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nights with pain, %</td>
<td>30.4</td>
<td>32.7</td>
<td>22.2‡</td>
<td>27.1</td>
</tr>
<tr>
<td>Average pain severity per night*</td>
<td>0.45</td>
<td>0.49</td>
<td>0.32‡</td>
<td>0.41</td>
</tr>
<tr>
<td>Antacid use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days used, %</td>
<td>37.1</td>
<td>41.6</td>
<td>24.6</td>
<td></td>
</tr>
<tr>
<td>Average number per day</td>
<td>1.24</td>
<td>1.35</td>
<td>0.72</td>
<td></td>
</tr>
</tbody>
</table>

*Severity was scored as follows: 0, none; 1, mild; 2, moderate; and 3, severe.
†P<.01 vs misoprostol.
‡P<.001 vs misoprostol.
§P<.05 vs misoprostol.
||P<.01 vs placebo.

Studies designed to evaluate ulcer prevention among long-term users of NSAIDs have varied regarding study design, data analysis, and results presented. Several trials with antisecretory drugs showed the outcome differed with gastric ulcers compared with duodenal ulcers and H pylori–infected ulcers compared with ulcers not infected with H pylori. None were randomized with regard to H pylori status. That is unfortunate since randomization would have ensured that if there were a difference in outcome in relation to H pylori status, the overall results of the study would not hinge on the proportion of patients with (or without) the infection. A study conducted in Hong Kong of patients with bleeding ulcers who were long-term users of NSAIDs shows the importance of this stratification. Even though the background rate of H pylori infection is high in Hong Kong (>80%), the proportion of study patients with complicated ulcer and H pylori infection was only 45.5%. Similarly, reanalysis of the outcomes of the OMNIUM10 and ASTRONAUT18 trials showed that H pylori infection has an important impact on outcome. The lowest effective dose of misoprostol (400 µg/d) was superior to omeprazole (8.2% vs 16.6%, respectively, developed gastric ulcers) (P=.04) and low-dose ranitidine (150 mg twice daily) was equivalent to omeprazole (14.6% vs 11.6%, respectively) (P=.56) for the prevention of gastric ulcers in patients with unequivocal NSAID ulcers who were long-term users of NSAIDs. Among those with H pylori infection, misoprostol was similar to omeprazole (5.7% vs 9.2%, respectively) (P=.48), and omeprazole was superior to low-dose ranitidine (1.9% vs 17%, respectively) (P=.001).

The present study was designed to avoid those shortcomings by comparing 2 doses of a proton pump inhibitor (lansoprazole) with the full therapeutic dose of misoprostol and placebo in patients with unequivocal NSAID-associated ulcers. As with omeprazole, lansoprazole was superior to placebo, with no evidence of a major dose response effect. We confirmed that gastric ulcers recurred during the 12-week follow-up in a greater
obtain mal antisecretory activity that ensured any benefit from prevention of ulcer complications. In the large dose misoprostol, 800 µg/d, with 2 doses of lansoprazole. In the OMNIUM study. One difference was that the age of patients receiving placebo compared with those receiving lansoprazole is approximately 1% per month compared with approximately 1% to 2% per year in those with ulcer disease who have not experienced a complication, it seems likely that it might. Thus, failure to identify and treat H pylori infection in the MUCOSA study may have biased the outcome. Studies are needed to test whether a proton pump inhibitor can prevent life-threatening ulcer complications among long-term users of NSAIDs. Because misoprostol and antisecretory drugs act by different mechanisms and low-dose misoprostol is better tolerated than full-dose therapy (but has a lower rate of protection), the combination of low-dose misoprostol and a proton pump inhibitor might provide optimum results. Thus, the ideal comparison might be a proton pump inhibitor with or without low-dose misoprostol (eg, 400 µg/d) vs placebo. However, such studies are unlikely to be conducted if the COX-2 inhibitors prove to eliminate life-threatening NSAID ulcer complications.

This study also showed that lansoprazole has several theoretical and practical advantages over misoprostol, including once-a-day dosing and lack of adverse effects. Compliance is a significant problem with misoprostol because full dosage requires 4-times-daily dosing, and the proportion with gastrointestinal adverse effects is dose dependent. This observation was demonstrated in this study: compliance with misoprostol was significantly inferior to that with lansoprazole. When the effect of noncompliance on ulcer development was considered, the percentage of patients remaining free from gastroduodenal ulcer disease was approximately 2-fold higher with active treatment vs placebo. As expected, noncompliance was less of a problem with misoprostol in the OMNIUM study, because a lower dose was used. Thus, it is apparent that despite the statistical advantage of misoprostol over proton pump inhibitors for the prevention of ulcer relapse in long-term users of NSAIDs, there is little, if any, practical advantage.

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