Alendronate and Naproxen Are Synergistic for Development of Gastric Ulcers

David Y. Graham, MD; Hoda M. Malaty, MD, PhD

Background: Both alendronate sodium use and non-steroidal anti-inflammatory drug use are associated with gastric ulcers. The aim of this study was to investigate whether alendronate and naproxen are synergistic as causes of gastric ulcers.

Methods: We performed an endoscopist-blind, randomized, crossover, single-center comparison of 10 mg/d of alendronate sodium, 500 mg of naproxen sodium twice daily, or the combination taken orally for 10 days in volunteers aged 30 years or older. Videoendoscopy was used to evaluate the presence and degree of mucosal damage to the esophagus, stomach, or duodenal bulb before and after each treatment. There was a 1- to 4-week washout between evaluations.

Results: Twenty-six healthy volunteers participated (18 women and 8 men), aged 30 to 50 years. Gastric ulcers were present in 2 subjects receiving alendronate (8%), in 3 receiving naproxen (12%), and in 10 receiving both (38%) (P < .05 for the combination vs either drug alone).

Conclusions: Both alendronate and naproxen can cause gastric ulcers. The combination appears synergistic. Alendronate should be used with caution in those who simultaneously require nonsteroidal anti-inflammatory drugs.

Arch Intern Med. 2001;161:107-110

A

LENDRONATE sodium (Fosamax) is a primary amino-bisphosphonate used for the treatment of osteoporosis and Paget disease.1 The most common adverse effects associated with alendronate use are abdominal pain and discomfort. There have been a number of reports of esophageal damage associated with the amino-bisphosphonates, alendronate and pamidronate disodium.2-15 In a study of gastrointestinal toxicity in patients treated with 40 mg/d of alendronate sodium assessed by the same endoscopic techniques used to evaluate nonsteroidal anti-inflammatory drugs (NSAIDs), alendronate was shown to cause visible gastric mucosal injury in the majority of those studied.16 The gastric mucosal injury was deemed severe in 55% of those receiving alendronate (6 of 11), and in 1 patient (8%) an alendronate-associated acute gastric ulcer was seen. To date, 141 volunteers have been studied following the oral administration of alendronate in doses ranging from 5 to 40 mg/d and in durations of from 4 to 28 days (Table 1). Overall, 7% developed gastric ulcers16-23 (Table 1).

NSAIDs are known for their ability to cause gastric mucosal damage and ulceration.24 The target population for alendronate treatment and the population most likely to take NSAIDs are similar. Therefore, the present study was designed to determine whether the combination of alendronate and an NSAID had an adverse effect on the mucosa of the upper gastrointestinal tract.

RESULTS

Twenty-six healthy volunteers participated, including 18 women and 8 men ranging in age from 30 to 50 years. Gastric ulcers were present in 8% receiving alendronate (n = 2), in 12% of those receiving naproxen (n = 3), and in 38% of those receiving the combination of alendronate and naproxen (n = 10) (P < .05 for the combination vs either drug alone). Endoscopic scores for overall gastric mucosal damage are shown in Table 3. The median endoscopic score was 0 for the alendronate-alone arm, between B and C for the naproxen-alone arm, and D for the combination arm. The combination regimen resulted in a significantly

From the Department of Medicine, Veterans Affairs Medical Center and Baylor College of Medicine, Houston, Tex.
SUBJECTS AND METHODS

The study was an endoscopist-blind, crossover, randomized, single-center endoscopic study. All volunteers gave informed written consent in accordance with the guidelines of the Committee on Human Investigation at Baylor College of Medicine, Houston, Tex, and in accordance with the rules of the Helsinki Declaration. Subjects were assigned to receive in random order (1) alendronate sodium, 10 mg once a day; (2) naproxen sodium, 500 mg twice a day; or (3) the combination of alendronate 10 mg once a day and naproxen 500 mg twice a day for 14 days. Alendronate was dosed according to the labeling instructions. Following a normal screening endoscopy, subjects received study medications from the study coordinator each morning for 14 days and underwent follow-up endoscopy on the 15th day. At least 1 week elapsed between each arm of the crossover. Endoscopic evaluations of the gastric mucosa were made prior to each treatment period, and starting a new drug was delayed until there was complete healing of any visible lesions.

Entry criteria included subjects with endoscopically normal gastric and esophageal mucosa. The subjects had to be willing to abstain from alcohol, caffeine-containing beverages, tobacco, highly spiced foods, and all other medications, including all over-the-counter products (except oral contraceptives) from 72 hours prior to each baseline endoscopic examination until the end of each of the 3 treatment periods. Exclusion criteria included a history of peptic ulcer, gastroesophageal reflux disease, dysphagia, gastrointestinal bleeding, gastrointestinal surgery, gastrointestinal dysfunction that could interfere with drug absorption, and current or recent treatment with any histamine2 receptor antagonists, proton pump inhibitors, misoprostol, sulfalate, metoclopamide hydrochloride, antacids, vitamins, or laxatives. Subjects were prohibited from using aspirin or NSAIDs for the 2 weeks prior to entry.

Within 48 hours of enrolling in the study, each subject underwent a baseline endoscopic evaluation of the gastric mucosa, after having fasted from 12 midnight the night before. Only subjects who had normal esophageal, gastric, and duodenal bulb mucosa were allowed to participate. Videocapsule was repeated after 7 and 14 days of treatment. All endoscopic examinations were performed by the same gastroenterologist (D.Y.G.) who remained blinded to the treatment given. Scoring was done as the endoscope was advanced. The esophagus, stomach, and duodenal bulb were scored separately using a standard scoring system that minimizes trivial damage such as mucosal hemorrhages (Table 2). The endoscopic scoring system has previously been validated. An erosion was defined as a lesion producing a definite discontinuity in the mucosa but having no depth. An ulcer was defined as any lesion measuring 3 mm or more with depth.

The endoscopic scores were compared using the Kruskal-Wallis 1-way analysis of variance on ranks (the normality test failed) with all multiple pairwise comparisons being done by the Student-Newman-Keuls method. Categorical data were analyzed by the χ2 statistic. All analyses were done using SigmaStat 2.03 software (SPSS Inc, Chicago, Ill).

higher degree of gastric damage than either drug alone (P<.05). In addition, treatment with naproxen alone was significantly more injurious than alendronate alone (P<.05).

No esophageal injury was seen in any group. Duodenal injury was mild but was significantly more common in the alendronate-naproxen group than with the alendronate-alone group (P<.05).

Naproxen was significantly better tolerated than either alendronate or the combination of alendronate and naproxen. Side effects were mild and were reported in only 6 volunteers receiving naproxen compared with 14 receiving alendronate, and 18 receiving both (P<.05 for naproxen vs alendronate or alendronate plus naproxen). The side effects reported for each treatment arm were as

Table 1. Results of Endoscopic Studies of Bisphosphonates in Relation to Gastric Ulcer Formation

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Dose, mg</th>
<th>Study Duration</th>
<th>Alendronate Sodium</th>
<th>Placebo, No. (% With Ulcer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanza et al</td>
<td>Alendronate</td>
<td>5</td>
<td>2 wk</td>
<td>22</td>
<td>1 (4.5), 22 (0)</td>
</tr>
<tr>
<td>Lanza et al</td>
<td>Alendronate</td>
<td>10</td>
<td>2 wk</td>
<td>21</td>
<td>2 (9.5), 22 (0)</td>
</tr>
<tr>
<td>Graham et al</td>
<td>Alendronate</td>
<td>10</td>
<td>2 wk</td>
<td>24</td>
<td>2 (8.2), 24 (0)</td>
</tr>
<tr>
<td>Herrera et al</td>
<td>Alendronate</td>
<td>5</td>
<td>4 wk</td>
<td>21</td>
<td>2 (9.5)*, 0</td>
</tr>
<tr>
<td>Lowe et al</td>
<td>Alendronate</td>
<td>5</td>
<td>4 wk</td>
<td>16</td>
<td>0, 16 (0)</td>
</tr>
<tr>
<td>Marshall et al</td>
<td>Alendronate</td>
<td>10</td>
<td>4 wk</td>
<td>25</td>
<td>2 (8.0), 25 (0)</td>
</tr>
<tr>
<td>Graham et al</td>
<td>Alendronate</td>
<td>40</td>
<td>4 d</td>
<td>12</td>
<td>1 (8.3), 12 (0)</td>
</tr>
<tr>
<td>Herrera et al</td>
<td>Pamidronate disodium</td>
<td>200</td>
<td>4 wk</td>
<td>19</td>
<td>0, 0</td>
</tr>
</tbody>
</table>

*Not completely clear in article regarding ulcers.

Table 2. Endoscopic Scoring System for Drug-Induced Mucosal Damage

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Mucosal Hemorrhages</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1 Area</td>
<td>&gt;1 Area</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Final Score</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>Normal (includes grade 1 mucosal hemorrhage)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Mucosal hemorrhages (grade 2 or higher)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>1 or 2 erosions</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>≥3 Areas with erosions</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Large areas of erosion with widespread involvement of the mucosa, or ulcer</td>
<td></td>
</tr>
</tbody>
</table>
follows: for the alendronate group, headache (6 subjects), loss of appetite/nausea (4 subjects), abdominal pain (3 subjects), diarrhea (2 subjects); for the naproxen group, headache (2 subjects), loss of appetite/nausea (5 subjects), abdominal pain (3 subjects), diarrhea (1 subject); and for the the alendronate-naproxen group, headache (2 subjects), loss of appetite/nausea (8 subjects), abdominal pain (8 subjects), and diarrhea (2 subjects).

The evidence is now overwhelming that use of alendronate alone can cause acute gastric ulcers (Table 1).

This study showed that the combination of alendronate and an NSAID was markedly more likely to produce severe gastric mucosal damage and symptoms than either drug given alone. The combination produced ulcers in more than one third of those studied. Naproxen has both a local effect and a systemic effect on the stomach. In contrast, alendronate is a topically caustic drug thought to cause gastric or esophageal mucosal damage by direct contact.

Why the combination of alendronate and an NSAID appears to be synergistic is unknown. Because NSAIDs reduce the rate of ulcer healing in the stomach or duodenum, it is possible that the NSAID slows healing and thus exaggerates the mucosal injury caused by alendronate. To test this hypothesis, it would be interesting to study whether NSAIDs also would accentuate the damage caused by other drugs known to cause topical gastric mucosal injury, such as the solid-dose forms of potassium.

The present study showed that subjects taking alendronate and the combination of alendronate and naproxen experienced side effects more often than those taking naproxen alone: 18 (69%) of those receiving alendronate plus naproxen reported side effects and 10 (38%) developed gastric ulceration. These results are consistent with an interview follow-up study of 813 women who filled prescriptions for alendronate. New symptoms referable to alendronate were reported by 32.8%, and 28.7% discontinued the drug, primarily because of gastrointestinal complaints. In that study, the risk of patients with an outpatient visit or hospitalization for an upper gastrointestinal complaint was more than one third of those studied. Naproxen has both a local effect and a systemic effect on the stomach. In contrast, alendronate is a topically caustic drug thought to cause gastric or esophageal mucosal damage by direct contact.

The combination produced ulcers in more than one third of those studied. Naproxen has both a local effect and a systemic effect on the stomach. In contrast, alendronate is a topically caustic drug thought to cause gastric or esophageal mucosal damage by direct contact.

Why the combination of alendronate and an NSAID appears to be synergistic is unknown. Because NSAIDs reduce the rate of ulcer healing in the stomach or duodenum, it is possible that the NSAID slows healing and thus exaggerates the mucosal injury caused by alendronate. To test this hypothesis, it would be interesting to study whether NSAIDs also would accentuate the damage caused by other drugs known to cause topical gastric mucosal injury, such as the solid-dose forms of potassium.

Studies in animals have shown that following the administration of indomethacin, alendronate may cause acute mucosal damage similar to that seen with aspirin or other NSAIDs. The data from animal and human studies suggest that bisphosphonates with primary amino side chains (primary amino-bisphosphonates), such as alendronate and pamidronate, may have increased potential to cause gastric damage. Risedronate sodium is not a primary amino-bisphosphonate, and studies comparing the effects of alendronate and risedronate on the gastroduodenal mucosa are currently in progress. Preliminary results using the doses prescribed for Paget disease have not reported a major difference in the development of ulcers.

Both alendronate and NSAIDs can cause gastric ulcers and one would therefore expect alendronate use to be associated an increase in gastroduodenal complications of ulcer disease. Yet, prospective studies have not reported an increase in ulcer complications. It is important to note that if the risk of gastroduodenal complications associated with alendronate use is about the same order of magnitude as with NSAIDs (eg, 1%-2% per year), an association could easily be missed unless large epidemiologic studies were done. At the same time, one should also note that use of potassium chloride, which also causes acute gastric mucosal damage, appears to be associated with a low risk of gastroduodenal ulcer complications. It remains unclear whether the gastrointestinal risks associated with alendronate are more akin to that seen with NSAIDs or with potassium. Further studies are warranted. Whatever the mechanism, until epidemiologic studies clearly show that alendronate use is not associated with an increased risk of ulcer complications, it would appear prudent not to prescribe anti-inflammatory doses of traditional NSAIDs to patients receiving alendronate (and vice versa). This study did not address the effect of coadministration of a selective cyclo-oxygenase 2 inhibitor instead of a traditional NSAID.

Accepted for publication July 28, 2000.

Corresponding author and reprints: David Y. Graham, MD, Veterans Affairs Medical Center (111D), 2002 Holcombe Blvd, Houston, TX 77030.

REFERENCES

REFERENCES


Correction

Errors in Reporting Treatment Duration. In the Original Investigation by Graham and Malaty titled “Alendronate and Naproxen Are Synergistic for Development of Gastric Ulcers,” published in the January 8, 2001, issue of the ARCHIVES (Arch Intern Med. 2001;161:107-110), the number of days of treatment was reported incorrectly. On page 108, lines 10 and 13 of the first paragraph of the “Subjects and Methods” section, the number of days should have read 10, and line 14 should have read “11th day.” In the sixth line of the third paragraph of the same section, the sentence should have read “Videoendoscopy was repeated after 10 days of treatment.” In Table 3 on page 109, the title should have read “Endoscopic Scores for Mucosal Damage After 10 Days of Drug Therapy.”