14 Day Endoscopy Study Comparing Risedronate and Alendronate in Postmenopausal Women Stratified by *Helicobacter pylori* Status

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ABSTRACT. ***Objective.*** Bisphosphonates are effective treatment for osteoporosis but have been associated with gastrointestinal (GI) mucosal injury. This study compared the incidence of gastric ulcers after treatment with risedronate, a pyridinyl bisphosphonate, or alendronate, a primary amino bisphosphonate, in healthy postmenopausal women stratified by *Helicobacter pylori* status.

Methods. Subjects were randomized to receive risedronate 5 mg (n = 318) or alendronate 10 mg (n = 317) daily for 14 days. Endoscopy and evaluator-blind assessments of the esophageal, gastric, and duodenal mucosa were performed at baseline and on Days 8 and 15.

Results. Overall, gastric ulcers ≥ 3 mm were observed in 18 (6.0%) of 300 evaluable subjects in the risedronate group and 36 (12.1%) of 297 in the alendronate group during treatment ($p = 0.013$). On Day 8, the incidences of gastric ulcers in the risedronate and alendronate groups were 3.6% and 6.6%, respectively ($p = 0.133$), and on Day 15, they were 3.3% and 8.7% ($p = 0.008$). The incidence of gastric ulcers was not affected by *H. pylori* status. Mean gastric endoscopy scores at Days 8 and 15 were significantly lower in the risedronate group than in the alendronate group ($p < 0.001$). Mean esophageal and duodenal endoscopy scores were similar in the 2 groups at Days 8 and 15. When the treatment groups were combined, gastric endoscopy scores were significantly higher among *H. pylori* negative than *H. pylori* positive subjects at Days 8 and 15 ($p < 0.05$). Upper GI adverse events were reported by 18 (5.7%) subjects in the risedronate group (19 events) and 28 (8.8%) subjects in the alendronate group (32 events). Symptoms did not predict the presence of mucosal damage.

Conclusion. Risedronate was associated with a significantly lower incidence of gastric ulcers than alendronate. *H. pylori* infection did not increase the incidence of bisphosphonate related gastric ulcers. The findings from this 14 day study in healthy volunteers support the hypothesis that bisphosphonates may differ from one another in their potential to produce upper GI mucosal damage. (J Rheumatol 2002;29:1965–74)

Key Indexing Terms:
OSTEOPOROSIS STOMACH ULCER ALENDRONATE
RISEDRONATE ENDOSCOPY

Bisphosphonates are effective therapy for the prevention and treatment of osteoporosis. These compounds inhibit bone resorption and increase bone mineral density, thereby reducing the incidence of osteoporotic fracture[1]. Bisphosphonates are generally well tolerated, although some have been associated with esophageal and gastric complications[2-5]. The pyridinyl bisphosphonate risedronate has been shown in clinical trials in over 15,000 patients to have a safety profile similar to that of placebo[6-12]. These studies enrolled a broad range of patients, including those with previous or active gastrointestinal (GI) disease, those requiring antisecretory therapy, and those receiving concomitant treatment with aspirin or nonsteroidal antiinflammatory drugs (NSAID). Risedronate was not associated with an increased frequency of adverse GI effects, even among subgroups of patients at high risk for these events[13,14]. The primary amino bisphosphonate alendronate has also been shown in large clinical trials to have a safety profile similar to that of placebo[15-17], although postmarketing data have revealed a higher than expected frequency and severity of GI side effects[3,18,19]. These findings may be related to the exclusion from alendronate trials of patients

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Supported by Procter & Gamble Pharmaceuticals, Mason, Ohio, and Aventis Pharma, Bridgewater, New Jersey.

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Submitted July 9, 2001; revision accepted February 22, 2002.

with upper GI disease[16,20,21], use of medications that could cause GI irritation[16,17], and daily treatment for dyspepsia[20]. Also, the clinical trial setting may be associated with greater compliance with dosing instructions than would be seen in clinical practice.

In recent endoscopy studies, alendronate has been associated with mucosal irritation[22-27]. Preclinical and clinical evidence suggests that mucosal irritation is more commonly associated with primary amino bisphosphonates than with pyridinyl bisphosphonates, suggesting that differences in structure may account for differences in the potential to irritate the GI mucosa. Blank, *et al* compared the gastric effects of nitrogen-containing bisphosphonates in an indomethacin treated rat model[28]. Antral damage (lesion length) was significantly greater in rats treated with alendronate or pamidronate, both primary amino bisphosphonates, than with the pyridinyl bisphosphonate risedronate. In a direct comparison of the upper GI effects of daily treatment for 2 weeks with risedronate 5 mg and alendronate 10 mg in 515 healthy postmenopausal women, gastric ulcers occurred in significantly more subjects treated with alendronate (13.2%) than with risedronate (4.1%)[29]. In a study of 66 postmenopausal women who had discontinued alendronate because of upper GI adverse events, risedronate 5 mg/day for 3 months was as well tolerated as placebo[30]. These studies support the premise that bisphosphonates differ in their potential to injure the GI mucosa, although the apparently lower GI toxicity of risedronate has to be confirmed through longterm use in routine clinical practice.

Infection with *Helicobacter pylori* is well recognized to cause upper GI injury, including peptic ulcer disease[31,32]. In previous small endoscopy studies of nitrogen bisphosphonates, no correlation between *H. pylori* infection and bisphosphonate related injury has been reported[22,23,26,33]; however, these studies may have been underpowered to detect an effect. More information is available about the effect of *H. pylori* infection on NSAID associated GI damage, but findings have been inconsistent. Effects have ranged from slight protection[34] to no influence[35-40] to potentiation[41-45]. Because *H. pylori* infection is common and its prevalence increases with age[46], its influence on bisphosphonate associated GI toxicity is relevant.

We conducted this 14 day endoscopy study to compare the effects of treatment with risedronate and alendronate on the mucosa of the upper GI tract, using the currently marketed wax polished oval alendronate tablets and the currently marketed risedronate tablets. The primary objective was to assess the incidence of gastric ulcers in healthy postmenopausal women orally administered risedronate 5 mg/day or alendronate 10 mg/day. The secondary objective was to assess the esophageal, gastric, and duodenal mucosa using validated endoscopic scoring systems. Subjects were stratified by *H. pylori* status to allow investigation of the influence of this factor on study outcomes.

MATERIALS AND METHODS

Study design. This was a 14 day, randomized, evaluator-blind endoscopy study conducted at 7 centers in the United States and Canada. The study was approved by the institutional review board or independent ethics committee of each center. The study was conducted in accord with the International Conference on Harmonization Guidelines and the Declaration of Helsinki and its amendments, as applicable.

Subjects. Healthy postmenopausal women at least 40 years of age were eligible to enroll if they had a normal esophageal and gastroduodenal mucosa at the screening endoscopy. Subjects were required to be nonsmokers and not to have used cigarettes, cigars, or a pipe within the 12 months preceding enrollment. They were required to abstain from using nicotine products and from ingesting alcohol or vitamin/mineral supplements during the study. For 2 weeks prior to the study and throughout the study, subjects were required to abstain from taking any drugs with a potential to induce upper GI irritation, such as aspirin or NSAID, or other medication considered by the investigator to contraindicate participation in this study. Subjects were excluded if they had a history of symptomatic upper GI ulcer, erosive esophagitis, an esophageal abnormality that delayed esophageal emptying, GI bleeding, or GI surgery, or if they had a significant coexisting illness that contraindicated administration of the study drugs or endoscopic evaluation. Subjects were also ineligible if they had taken any bisphosphonate drug in the previous 4 months. All subjects provided written informed consent.

Treatment. Subjects were screened for eligibility within 14 days of the start of treatment. At the screening visit, subjects gave a medical history, underwent physical examination, and provided specimens for laboratory evaluations. Eligible subjects underwent endoscopy, and the appearance of the mucosa of the esophagus, stomach, and duodenum was evaluated and scored (Table 1). The presence or absence of *H. pylori* infection was determined for each subject with a ^{13}C-urea breath test (Meretek Diagnostics, Inc., Nashville, TN, USA)[47].

After screening, eligible subjects at each study center were stratified according to *H. pylori* status (positive or negative) and randomly assigned to receive risedronate 5 mg or alendronate 10 mg on the basis of a blocked randomization schedule provided by the sponsor. Risedronate was supplied as commercially available film coated 5 mg tablets. Subjects were instructed to take one risedronate tablet once daily with 4 or more ounces (≥ 120 ml) of plain water at least 30 min before the first food or beverage of the day and not to lie down for 30 min after taking the tablet. Alendronate was supplied as the currently marketed wax polished oval 10 mg tablets. Subjects were instructed to take one alendronate tablet once daily with 6 to 8 ounces (180–240 ml) of plain water at least 30 min before the first food, beverage, or medication of the day. They were told not to lie down for at least 30 min after taking the tablet and until after their first food of the day. Subjects were to take their study medications for 14 days and to record on a diary card each time they took their study medication. To preserve the study blind, personnel who were not involved in subject evaluations dispensed the study medications. Treatment compliance was determined by tablet count and by information noted on the diary cards. Subjects in either treatment group were considered compliant with treatment if they were 100% compliant on Days 6, 7, 13, and 14 and at least 80% compliant on Days 1 to 5 and 8 to 12.

On Day 1, eligible subjects with normal endoscopic findings were given a 14 day supply of study medication and a diary card, which provided written dosing instructions and a place to record each time the medication was taken. On Day 8, after 7 days of treatment, and Day 15, after 14 days of treatment, subjects returned to the study site for repeat endoscopy. In addition, subjects were asked whether they had experienced any changes in well being. Adverse events were recorded for each subject throughout the study.

Endoscopic evaluations. The esophageal, gastric, and duodenal mucosa was evaluated endoscopically at screening and again on Days 8 and 15. For each subject, the same endoscopist performed the evaluations at Days 8 and

Table 1. Endoscopic grading scales used in evaluating the condition of the mucosa in the esophagus* and stomach and duodenum†.

Grade	Description
Esophagus	
0	Normal mucosa (no abnormalities noted)
1	Erythema, hyperemia, and/or friability present (no macroscopic erosions visible)
2	Superficial ulcerations** or erosions†† involving < 10% of the mucosal surface area on the last 5 cm of esophageal squamous mucosa
3	Superficial ulcerations or erosions involving ≥ 10% but < 50% of the mucosal surface area on the last 5 cm of esophageal squamous mucosa
4	Deep ulceration anywhere in the esophagus or confluent erosion of > 50% of the mucosal surface area on the last 5 cm of esophageal squamous mucosa
5	Stricture that precludes the passage of the endoscope (if present, the subject was discontinued from the study)
Stomach and duodenum	
0	No visible lesions (i.e., hemorrhages***, erosions, or ulcers)
1	Mucosal hemorrhages only (≤ 25)
2	1 to 2 erosions, or > 25 hemorrhages
3	3 to 9 erosions
4	≥ 10 erosions or an ulcer

* Reprinted from reference 48 with permission (Gastroenterology 1988; 95: 904). † Reprinted from reference 22 with permission from the American College of Gastroenterology (American Journal of Gastroenterology 1998; 93: 754). ** Ulcer was defined as a break in the mucosa (≥ 3 mm in diameter) with apparent depth. Ulcer diameter was estimated by apposition of endoscopic forceps with defined dimensions. †† Erosion was defined as an erythematous superficial mucosal defect that disrupted the epithelium and was not an ulcer as described above. *** Hemorrhage was defined as a red spot with no mucosal defect.

15. Investigators and other personnel participating in the endoscopic evaluations were blinded to the subjects' treatment. The esophageal mucosa was assessed using the Hetzel-Dent grading/scoring system[48] (Table 1). The gastric and duodenal mucosa was assessed using the Lanza grading system[22] (Table 1). Erosions were defined as erythematous superficial mucosal defects that disrupted the epithelium and were not ulcers. Ulcers were defined as breaks in the mucosa ≥ 3 mm in diameter with apparent depth[29]. Ulcer diameter was estimated by apposition of endoscopic forceps with defined dimensions. Photographs were taken of each site (esophagus, stomach, duodenum) and of all ulcers at the Day 8 and Day 15 endoscopic evaluations.

Data analysis. Analyses of endoscopic data, including ulcer incidence and endoscopy scores, were based on evaluable subjects. The evaluable population was determined separately for Day 8 and Day 15. Subjects were considered evaluable if they completed the endoscopic evaluations at Day 8 or 15, met the criteria for compliance with study drug, and had not been major protocol violators up to that visit day. The evaluable population for the overall analysis of the 14 day treatment period included subjects who were evaluable at both Day 8 and Day 15. An intent-to-treat analysis of endoscopic findings for all subjects who received at least one dose of study drug was also performed. The analysis of adverse events included data from all subjects who received at least one dose of study drug. The 7 investigator sites were pooled by geographic region to form 4 pooled centers before the data were unblinded.

The overall incidence of gastric ulcers during the 14 day treatment period was compared between the 2 treatment groups using an exact test stratified by *H. pylori* status and pooled center (StatXact, Cytel Software Corp., Cambridge, MA, USA). Ninety-five percent exact confidence intervals were constructed for the odds ratio and for the difference in the incidence of gastric ulcer between the 2 treatment groups. The homogeneity of the OR across the strata defined by *H. pylori* status and pooled center was assessed by Zelen's exact homogeneity test (StatXact). These analyses were also used to compare the treatment groups with respect to the incidence of gastric ulcers observed separately at Day 8 and Day 15. Subjects who did not continue in the study after their Day 8 endoscopic evaluation were not included in the analysis at Day 15. The overall incidence of gastric ulcers ≥ 5 mm in diameter during the 14 day treatment period was compared between the 2 treatment groups using Fisher's exact test.

A secondary objective of the study was to assess the esophageal and gastroduodenal mucosa using the described endoscopy scores. A nonparametric Wilcoxon rank-sum test was used to compare the 2 treatment groups with respect to these scores.

The overall incidence of gastric ulcers was also compared between the risedronate and alendronate groups with Fisher's exact test for each subgroup of *H. pylori* positive and negative subjects, and p values were provided. The incidence of gastric ulcers was also compared between the *H. pylori* positive and negative subjects with Fisher's exact test. The gastric endoscopy scores were summarized and compared between the risedronate and alendronate groups with the nonparametric Wilcoxon rank-sum test for each subgroup of *H. pylori* positive and negative subjects. The same test was used to compare gastric endoscopy scores between the *H. pylori* positive group and the *H. pylori* negative group.

All statistical tests were conducted against a 2 sided alternative hypothesis, employing a significance level of 0.05.

The sample size provided 90% power to detect an 8% difference between alendronate and risedronate in the overall incidence of gastric ulcers during the 14 day treatment period. This calculation was based on the assumption that the incidence of gastric ulcers is 13% for alendronate and 5% for risedronate[22,29].

RESULTS

Subjects. A total of 635 subjects were randomly assigned to receive risedronate (n = 318) or alendronate (n = 317). The treatment groups were similar with respect to demographic characteristics and history except that a higher percentage of subjects in the alendronate group had used tobacco prior to the 12 months preceding enrollment (p = 0.03) (Table 2). Of 632 subjects with at least one postbaseline endoscopy, 165 (26.1%) were *H. pylori* positive and 467 (73.9%) were *H. pylori* negative. The percentages of subjects positive for *H. pylori* were similar in the risedronate (25.6%) and alendronate (26.7%) groups. A total of 38 subjects (18 risedronate group, 20 alendronate group) did not meet the

Table 2. Baseline characteristics of the subjects by treatment group.

	Risedronate, N = 318	Alendronate, N = 317	p*
Age, yrs			
Mean ± SD	54.8 ± 7.5	54.7 ± 7.1	0.943
Range	40–80	40–82	
Weight, lb			
Mean ± SD	160.8 ± 34.2	165.3 ± 34.8	0.098
Range	99–330	110–284	
Height, in			
Mean ± SD	64.7 ± 2.7	64.7 ± 2.5	0.908
Range	54–71	59–72	
Race, No. subjects (%)			
Caucasian	275 (86.5)	279 (88.0)	0.084
Black	28 (8.8)	26 (8.2)	
Other†	15 (4.7)	12 (3.8)	
Tobacco usage, No. subjects (%)			
Never	218 (68.6)	189 (59.6)	0.015
Previously	100 (31.4)	128 (40.4)	
Alcohol consumption, No. subjects (%)			
Never	75 (23.6)	78 (24.6)	0.805
Previously	54 (17.0)	48 (15.1)	
Currently	189 (59.4)	191 (60.3)	

* Comparison of risedronate and alendronate, adjusting for pooled center and *H. pylori* status, using an analysis of variance model for age, weight, and height and Cochran-Mantel-Haenszel for race, tobacco usage, and alcohol consumption.

† Includes Asian Oriental, Hispanic, Asian Indian, and multiracial.

criteria for evaluability and were excluded from the overall analysis of endoscopy data. The most common reason for exclusion was the use of drugs prohibited by the protocol.

Endoscopic observations. The overall incidence of gastric ulcers ≥ 3 mm in diameter, the primary endpoint for the study, was significantly greater in the alendronate group than in the risedronate group (p = 0.013) (Table 3). Gastric ulcers were observed during the 14 day treatment period in 18 (6.0%) subjects in the risedronate group, compared with 36 (12.1%) subjects in the alendronate group. The odds of developing a gastric ulcer over the 14 day treatment period were 2.2 times higher in the alendronate group compared to the risedronate group (95% CI 1.2 to 4.0). The heterogeneity of odds ratios across the strata defined by *H. pylori* status and pooled center was not statistically significant. Gastric ulcers ≥ 5 mm in diameter were noted in 3.3% of subjects in the risedronate group, compared with 7.7% of subjects in the alendronate group (p = 0.02). Most gastric ulcers whose locations were recorded were noted in the antrum.

The incidence of gastric ulcers observed at Day 8 was lower in the risedronate group than in the alendronate group, but the difference was not statistically significant (p = 0.133) (Table 3). The incidence of gastric ulcers observed at Day 15 was significantly lower in the risedronate group than in the alendronate group (p = 0.008). Gastric ulcers were noted at both Day 8 and Day 15 in 2 subjects in the rise-

Table 3. Incidence of gastric ulcers.

		Rosedronate			Alendronate			Alendronate vs Risedronate			
								Odds Ratio		Percent Difference	
Visit	N	n (%)	95% CI (%)	N	n (%)	95% CI (%)	p *	Estimate	95% CI†	Estimate	95% CI (%)**
Overall††	300	18 (6.0)	3.6, 9.3	297	36 (12.1)	8.6, 16.4	0.013	2.2	1.2, 4.0	6.1	0.7, 11.8
Day 8	305	11 (3.6)	1.8, 6.4	301	20 (6.6)	4.1, 10.1	0.133	1.9	0.9, 4.2	3.0	–1.4, 7.7
Day 15	302	10 (3.3)	1.6, 6.0	300	26 (8.7)	5.7, 12.4	0.008	2.8	1.4, 6.3	5.4	0.7, 10.3

N: number of subjects randomized to treatment who had a gastric endoscopic evaluation at the visit; n (%): number and percentage of subjects at the visit with at least one ulcer.

* Comparison of risedronate and alendronate using an exact test stratified by *H. pylori* status and pooled center.

† 95% CI for odds ratio based on exact conditional method.

** 95% CI for percent difference based on exact unconditional method.

†† A subject was evaluable overall if she was evaluable at both Day 8 and Day 15.

dronate group and 9 in the alendronate group. The heterogeneity of odds ratios across the strata defined by *H. pylori* status and pooled center was not statistically significant at either Day 8 or Day 15. Gastric erosions were also observed less frequently in the risedronate group than in the alendronate group overall and at Days 8 and 15 (data not shown).

Gastric ulcer incidence was also higher in the alendronate group than in the risedronate group in both *H. pylori* positive and negative subjects. Among *H. pylori* positive subjects, gastric ulcers were noted in 3 (3.9%) subjects in the risedronate group, compared with 11 (13.9%) in the alendronate group ($p < 0.05$). Among *H. pylori* negative subjects, gastric ulcers were noted in 15 (6.7%) subjects in the risedronate group, compared with 25 (11.5%) in the alendronate group ($p = 0.098$). When the risedronate and alendronate groups were combined, the incidence of gastric ulcers was 9.0% among both *H. pylori* positive and *H. pylori* negative subjects.

The percentages of subjects with esophageal hemorrhages, erosions, and ulcers were similar in the 2 treatment groups. Esophageal ulcers were noted in 3 subjects. In the risedronate group, one esophageal ulcer was noted in one subject (Hetzel-Dent score of 4), and in the alendronate group, one esophageal ulcer was noted in one subject (Hetzel-Dent score 2) and 2 esophageal ulcers were noted in a second subject (Hetzel-Dent score 3).

The percentages of subjects with duodenal hemorrhages and erosions were also similar in the 2 treatment groups. Duodenal ulcer was observed in only one subject. This was one subject in the risedronate group who was noted to have a duodenal ulcer at Day 8 (Lanza score 4) but not at Day 15. This subject was excluded from the evaluable population because her baseline endoscopy findings were abnormal.

Endoscopy scores. Gastric endoscopy scores were significantly lower in the risedronate group than in the alendronate group at both Day 8 and Day 15 ($p < 0.001$ for both time points) (Table 4). At Day 8, gastric endoscopy scores were 2 or greater in 21.0% of the subjects in the risedronate group, compared with 36.2% of the subjects in the alendronate group. At Day 15, gastric endoscopy scores were 2 or greater in 19.2% of the subjects in the risedronate group, compared with 38.0% of the subjects in the alendronate group.

Esophageal endoscopy scores were similar in the risedronate and alendronate groups at Day 8 ($p = 0.067$) and Day 15 ($p = 0.991$) (Table 4). At Day 8, esophageal endoscopy scores were 2 or greater in 2.3% of subjects in the risedronate group and 3.0% in the alendronate group. At Day 15, esophageal endoscopy scores were 2 or greater in 5.0% of subjects in the risedronate group and 4.7% in the alendronate group. Duodenal endoscopy scores were similar in the risedronate and alendronate groups at both Day 8 ($p = 0.189$) and Day 15 ($p = 0.781$) (Table 4). Duodenal endoscopy scores of 2 or greater were noted in 4.6% of subjects in the risedronate group and 4.3% in the alen-

Table 4. Number (%) of subjects with individual erosion scores.

Site and Erosion Score	Day 8 Risedronate, n = 305	Day 8 Alendronate, n = 301	Day 15 Risedronate, n = 305	Day 15 Alendronate, n = 301
Esophagus				
0	297 (97.4)	284 (94.4)	281 (93.0)	279 (93.0)
1	1 (0.3)	8 (2.7)	6 (2.0)	7 (2.3)
2	6 (2.0)	9 (3.0)	12 (4.0)	11 (3.7)
3	1 (0.3)	0 (0.0)	2 (0.7)	3 (1.0)
4	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mean ± SEM	0.05 ± 0.02	0.09 ± 0.02	0.13 ± 0.03	0.13 ± 0.03
Stomach				
0	203 (66.6)	162 (53.8)	205 (67.9)	150 (50.0)
1	38 (12.5)	30 (10.0)	39 (12.9)	36 (12.0)
2	23 (7.5)	36 (12.0)	26 (8.6)	27 (9.0)
3	28 (9.2)	49 (16.3)	22 (7.3)	56 (18.7)
4	13 (4.3)	24 (8.0)	10 (3.3)	31 (10.3)
Mean ± SEM	0.72 ± 0.07*	1.15 ± 0.08	0.65 ± 0.06*	1.27 ± 0.09
Duodenum				
0	272 (89.2)	278 (92.4)	279 (92.4)	279 (93.0)
1	19 (6.2)	10 (3.3)	13 (4.3)	11 (3.7)
2	7 (2.3)	9 (3.0)	4 (1.3)	3 (1.0)
3	6 (2.0)	3 (1.0)	5 (1.7)	7 (2.3)
4	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)
Mean ± SEM	0.18 ± 0.03	0.14 ± 0.03	0.13 ± 0.03	0.13 ± 0.03

* Significantly different from alendronate, $p < 0.001$, nonparametric Wilcoxon rank-sum test.

dronate group at Day 8, and in 3.3% of the subjects in each group at Day 15.

When the subgroups of *H. pylori* positive and *H. pylori* negative subjects were analyzed, the results of comparisons of endoscopy scores between the risedronate and alendronate groups were generally similar to those for the population of *H. pylori* positive and *H. pylori* negative subjects combined for the esophagus (data not shown), stomach (Table 5), and duodenum (data not shown).

When the risedronate and alendronate groups were combined, and the groups of *H. pylori* positive and negative subjects were compared, the gastric endoscopy scores were significantly higher among *H. pylori* negative subjects than among *H. pylori* positive subjects at both Day 8 (mean score, 0.66 for *H. pylori* positive subjects vs 1.03 for *H. pylori* negative subjects; $p < 0.05$) and Day 15 (mean score, 0.68 for *H. pylori* positive subjects vs 1.06 for *H. pylori* negative subjects; $p < 0.05$).

Adverse events. Adverse events were reported by 75 (23.6%) subjects in the risedronate group and by 89 (28.1%) in the alendronate group. The number of adverse events reported was lower among risedronate treated subjects (126 events) than among alendronate treated subjects (150 events). The most frequently reported treatment-emergent adverse events reported during the study were headache and dyspepsia (Table 6). One subject in the risedronate group discontinued the study because of chest pressure, which was considered doubtfully related to study treatment. Eighteen (5.7%) subjects in the risedronate group reported 19 upper GI events, and 28 (8.8%) subjects in the alendronate group reported 32 upper GI adverse events. The upper GI adverse events reported consisted of dyspepsia, abdominal pain, and GI disorder (regurgitation and esophageal reflux). Most events were mild or moderate in severity. However, 2 severe (subject could not perform normal activities) upper GI adverse events (abdominal pain and dyspepsia) were noted in subjects receiving alendronate. There was no correlation between the occurrence of GI symptoms and incidence of gastric ulcer.

DISCUSSION

When administered daily for 14 days to healthy volunteers at doses approved for the treatment of osteoporosis, risedronate was associated with a significantly lower incidence of gastric ulcers than alendronate. Gastric ulcers were observed in 18 (6.0%) subjects in the risedronate group, compared with 36 (12.1%) subjects in the alendronate group ($p = 0.013$) during the 14 day treatment period. The odds of developing a gastric ulcer over the 14 day treatment period were 2.2 times higher in the alendronate group than in the risedronate group. In addition, the percentage of subjects with ulcers $\geq$ 5 mm in diameter was also significantly lower in the risedronate group ($p = 0.02$). This could be clinically significant since aspirin-associated gastric ulcers more than 5 mm in diameter may be slower to heal and more resistant to medical therapy than smaller ulcers[49]. Gastric endoscopy scores (a secondary endpoint of the study) were also significantly lower in the risedronate group than in the alendronate group at both Day 8 and Day 15. The intent-to-treat analysis of data from all subjects who received at least one dose of study drug yielded similar results (data not shown). These results are consistent with those of a similar study[29] in which gastric ulcers were observed during the 14 day treatment period in 4.1% of subjects in the risedronate 5 mg

Table 5. Mean ± SEM gastric erosion scores at Days 8 and 15 for subgroups of *H. pylori* positive and *H. pylori* negative subjects.

	H. pylori Positive Subjects			*H. pylori* Negative Subjects		
Timepoint	Risedronate	Alendronate	p *	Risedronate	Alendronate	p*
Day 8	0.41± 0.10	0.90 ± 0.16	0.051	0.83 ± 0.08	1.23 ± 0.09	0.002
Day 15	0.48 ± 0.11	0.86 ± 0.15	0.076	0.71± 0.08	1.42 ± 0.10	< 0.001

* Comparison of risedronate and alendronate by nonparametric Wilcoxon rank-sum test.

Table 6. Summary of most frequently reported (> 2%) treatment-emergent adverse events.

	Risedronate, N = 318		Alendronate, N = 317	
Adverse Event	No. of Subjects (%)	No. of Events Reported	No. of Subjects (%)	No. of Events Reported
Headache	21 (6.6)	26	24 (7.6)	27
Dyspepsia	12 (3.8)	12	16 (5.0)	17
Nausea	10 (3.1)	10	13 (4.1)	13
Diarrhea	11 (3.5)	11	11 (3.5)	11
Abdominal pain	6 (1.9)	7	11 (3.5)	13
Flatulence	6 (1.9)	6	8 (2.5)	8

group, compared with 13.2% in the alendronate 10 mg group ($p < 0.001$). The similarity in the results of these 2 studies, despite differences between the alendronate formulations tested, suggests that ulcerogenic potential is inherent to the active ingredient common to the alendronate treatments used in both studies.

These findings support the hypothesis that nitrogen bisphosphonates differ in their potential to irritate the upper GI mucosa. Differences in chemical structure may result in differences in the GI toxicity of these agents. Such differences are apparent at the doses of risedronate and alendronate approved for treatment of postmenopausal osteoporosis[29]. Despite these differences in the severity and frequency of GI events, treatment with risedronate 5 mg and alendronate 10 mg appears to result in similar reductions in fracture risk[6,10,15,50]. However, there has been no head-to-head comparison of treatment efficacy. The lower GI toxicity of risedronate relative to alendronate observed in this short term study in healthy volunteers must be confirmed through longterm use in patients.

The presence of *H. pylori* infection did not increase the risk of bisphosphonate related gastric ulceration but did appear to influence gastric endoscopy scores (Table 5), suggesting a possible protective effect of *H. pylori* infection. When the risedronate and alendronate results were combined and the groups of *H. pylori* positive and negative subjects were compared, the mean gastric endoscopy scores were significantly higher among *H. pylori* negative subjects than among *H. pylori* positive subjects at both Days 8 and 15. Interestingly, in previous small endoscopy studies of bisphosphonates, the frequency of *H. pylori* infection was lower among subjects with gastric ulcers than would have been expected on the basis of the frequency of infection in the study population as a whole[22,23,26,27]. The mechanisms underlying *H. pylori* associated GI injury are complex and multifactorial. Injury appears to be related to the virulence of the infecting strain[51] and factors influencing host susceptibility, such as genotype and mucosal immune response[31,32]. The selection for our study of subjects with a normal GI mucosa at baseline may have introduced confounding factors that would preclude any definitive conclusions regarding the effect of *H. pylori* infection on bisphosphonate associated GI injury.

The complex dosing requirements for bisphosphonates have led to efforts to develop a more flexible dosing regimen. Administration of alendronate 70 mg in a once weekly regimen was approved recently in the United States for the treatment of osteoporosis. In an initial study, the overall incidence of upper GI adverse events associated with the once weekly regimen of alendronate 70 mg was similar to that associated with the daily regimen of alendronate 10 mg[52]. However, it remains to be seen whether less frequent administration of alendronate at a higher dose will lead to any change in alendronate associated mucosal damage. Since bisphosphonate induced mucosal injury appears to be topical[26,53,54] and dose related[22,28,55,56], the effects of higher local concentrations of the drug will need to be evaluated. Further, it is possible that gastric adaptation, which has been observed with daily exposure to aspirin[57] and in rats with daily administration of alendronate[58], may not occur with less frequent dosing. Despite the results of the initial study with alendronate 70 mg once weekly[52], we caution that the relative safety of weekly administration of alendronate should be carefully studied in its target population.

The results of this study are in contrast with 2 smaller endoscopy studies[33,59]. The first compared the effects of daily treatment with alendronate 40 mg or risedronate 30 mg on the upper GI mucosa in 235 men and women[33]. Gastric endoscopy scores after 28 days of treatment showed that risedronate and alendronate had a similar potential for gastric irritation. The second smaller study, in 32 women treated daily with alendronate 10 mg or placebo, also evaluated endoscopy scores after one month of treatment[59]. In that study, alendronate 10 mg/day did not cause upper GI mucosal damage. In both studies, endoscopic evaluation was performed after one month of treatment. Since alendronate associated mucosal injury occurs much earlier than 28 days after the start of therapy[22,23,25-27,29], endoscopic evaluation at 28 days may not reveal earlier GI injury. At later time points, gastric adaptation, if it occurs with exposure to bisphosphonates, may allow the resolution of early lesions. Short term endoscopy studies in which subjects were evaluated after 4 to 14 days of alendronate treatment have consistently revealed ulceration rates of 7% to 13%[22,23,25-27,29]. Further, postmarketing reports indicate that alendronate associated GI events frequently occur early in therapy, often within 7 days of the start of treatment[60,61]. The predictive value of lesions seen after 2 weeks of treatment for later serious adverse events is not known. Nevertheless, since there have been numerous reports of serious GI problems within 2 weeks of the start of alendronate treatment[3,62], it is important and clinically relevant that endoscopy studies evaluate the early GI effects of alendronate.

The mean age of subjects in our study was 55 years in both the risedronate and alendronate groups. Although this mean age is lower than that in patients with postmenopausal osteoporosis (e.g., Fracture Intervention Trial, average age 71 yrs[15]; Vertebral Efficacy with Risedronate Therapy Trial, average age 69 yrs[6]), it is similar to that of patients receiving treatment for the prevention of postmenopausal osteoporosis and prevention and treatment of glucocorticoid induced osteoporosis[7-9,63-65]. Aging is associated with impairment of gastric mucosal protective factors[66]. It has been suggested that aging itself may constitute an independent risk factor in the development of NSAID related gastropathy[66]. If susceptibility to bisphosphonate gastropathy is also increased in the elderly, our study findings are conservative, in that the

absolute rate of bisphosphonate associated injury might be greater among older patients in clinical practice.

In our study, the incidence of adverse events was higher in the alendronate group than in the risedronate group. However, there was no correlation between GI adverse events and endoscopic scores in either group. A lack of correlation between bisphosphonate associated GI symptoms and the severity of mucosal damage has also been reported by others[29,67]. Nevertheless, the clinical significance of silent mucosal injury cannot be overlooked. NSAID users who are hospitalized with serious GI complications often have had no GI events prior to the onset of the complications that led to hospitalization[68]. In clinical practice, bisphosphonates have been associated with clinically apparent esophageal lesions[3,62]. Such lesions have been attributed to contact between the bisphosphonate pill and the esophageal mucosa in patients who failed to comply with dosing instructions[3,62]. In our study, esophageal lesions were seen less frequently than gastric lesions, presumably because the subjects took their medication as instructed, and thus avoided prolonged esophageal exposure to the drug.

Conclusions

When administered for 14 days to healthy volunteers at doses for the daily treatment of osteoporosis, risedronate was associated with a significantly lower incidence of gastric ulcers than alendronate. These results are consistent with those of a previous similar study[29] despite differences between the studies in the shape and polish of the alendronate tablets. The presence of *H. pylori* infection did not increase the risk of bisphosphonate related gastric ulceration, but did appear to influence gastric endoscopy scores. Further study of the role of *H. pylori* infection on bisphosphonate associated mucosal injury is indicated. The findings from this study support the hypothesis that bisphosphonates differ in their potential to irritate the upper gastrointestinal mucosa when given at doses recommended for the treatment of osteoporosis.

APPENDIX

The following institutions and primary investigators participated in the Risedronate Endoscopy Study: J. Breiter, MD, P. Thibado, Center for Medical Research, Manchester, Connecticut; C. James, McMaster University Medical Centre, Hamilton, Ontario, Canada; F. Sutton, MD, M.F. Rack, Houston Institute for Clinical Research, Houston, Texas; M. Brannan, MD, A. Poch, MD, D. Philips, MD, K. Barnett, MD, D. Hatfield, Gastrointestinal Specialists AMC, Shreveport, Louisiana; E. Spiotta, MD, J. Hawkins, K. Hawkins, Southern Medical Research, Memphis, Tennessee; S. Appelman, University of Alberta, Edmonton, Alberta, Canada; S. Veldhuyzen van Zanten, MD, PhD, J. Love, MD, QEII Health Sciences Centre, Halifax, Nova Scotia.

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