

Clinic Visits and Hospital Admissions for Care of Acid-Related Upper Gastrointestinal Disorders in Women Using Alendronate for Osteoporosis

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Abstract

Context: About 1 in 3 women taking alendronate for osteoporosis report gastrointestinal symptoms, a rate much higher than that found during clinical trials.

Objective: To establish the frequency of outpatient visits and hospital admissions for acid-related upper gastrointestinal disorder (ARD) among women taking alendronate and to identify potential risk factors.

Methods: A retrospective database analysis identified 812 women with osteoporosis who had filled one or more 10-mg alendronate prescriptions from October 1995 through October 1996.

Results: One hundred (12.3%) of the 812 women received healthcare for ARD, a clinical encounter rate of 28.5 per 100 person-years. A reference group of 362,109 women from the same health plan had 17.6 ARD encounters per 100 person-years. Excluding women who had ARDs before receiving alendronate, alendronate users were 1.6 (95% CI=1.2, 2.7) times more likely to have an ARD encounter than nonusers. Risk of having ARD increased with age [users aged 70 years and older had a relative risk of 1.5 (95% confidence interval (CI) 1.0-2.30) compared with younger women] and with concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) (relative risk 1.7, 95% CI 1.1-2.6).

Conclusions: Elderly alendronate users or those concurrently taking NSAIDs should be carefully monitored because of their high risk of having ARD. Cost/benefit analyses of alendronate treatment for osteoporosis should include costs of treating ARD.

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We previously reported that 32.8% of women taking alendronate for treatment of osteoporosis reported gastrointestinal adverse events that they ascribed to use of the drug.¹ This frequency was much greater than has been reported in clinical trials.^{2,4} The difference in frequency could be due to differences in patient selection, lack of adherence to dosing safety rules, or concomitant use of other medications.

Clinical trials of alendronate have excluded women who have active upper gastrointestinal disease or who regularly use H₂ blockers.^{2,4} Some trials have excluded women who used nonsteroidal anti-inflammatory drugs (NSAIDs) or glucocorticoid drugs.^{2,3} In clinical practice, however, many women treated for osteoporosis use these drugs or have these conditions. Women receiving alendronate are usually elderly, and the prevalence of acid-related upper gastrointestinal disorder (ARD) increases with age.⁵ Disease prevalence among female members of the Kaiser Foundation Health Plan in northern California aged 65 years or older was 2.8% for gastroesophageal reflux disease, 6.0% for peptic ulcer disease, and 1.1% for gastritis/dyspepsia.⁵ We previously reported that among women starting alendronate treatment, use of other drugs concomitantly was common: concomitantly or within 6 months before alendronate was started, NSAIDs were prescribed for 34.2%, glucocorticoid drugs for 19.7%, and anti-ulcer drugs for 23.4%.¹

In clinical trials of alendronate, participants were likely to have received intensive and repeated counseling on the need to adhere to dosing instructions. Once the drug was in use in general practice, we found that of 812 women who had used it, 13.5% did not follow dosing safety rules such as taking alendronate with a sufficient amount of water, not chewing or sucking on the tablet, and remaining upright for 30 minutes after dosing.¹ On March 15, 1996, the manufacturer issued a letter warning physicians that alendronate can be irritating to the esophagus, but that careful adherence to the dosing instructions can reduce the potential

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for irritation.⁶ Compliance with instructions was slightly better after this warning letter was disseminated.

The purpose of our study was to determine rate of ARD among women using alendronate for osteoporosis and to assess whether ARD is influenced by potential risk factors. We hypothesized that in addition to the patient having a prior diagnosis of ARD, the following factors would increase the risk of requiring medical care for ARD in women receiving alendronate: age greater than 70 years, concurrent use of

NSAIDs, use of oral glucocorticoid drugs, or noncompliance with patient safety instructions.

... METHODS ...

Patient Selection

For the 2.6 million members of Kaiser Foundation Health Plan (KFHP) in northern California, we searched the computer database of all outpatient clinic visits, the database of all hospital discharge diagnoses, and the database of all prescriptions to locate patients who received ARD diagnoses (peptic ulcer, gastric ulcer, gastroesophageal reflux disease, gastritis, esophagitis, dyspepsia, nausea, vomiting, and abdominal pain) and who also received alendronate with or without recent or concomitant nonsteroidal anti-inflammatory drugs (NSAIDs) or oral glucocorticoid agents.

Thus, using the methods previously described,¹ we selected 812 women who began using alendronate during the period from October 1995 through October 1996. All subjects were contacted by telephone to confirm that they had taken the drug and to obtain information regarding adherence to patient dosing instructions.

We then examined the occurrence of ARD among all women health plan members for the first 9 months of 1996 by using the databases of outpatient clinic visits

Figure 1. Cumulative Probability (Percentage) of Discontinuing Alendronate by Month of Follow-Up

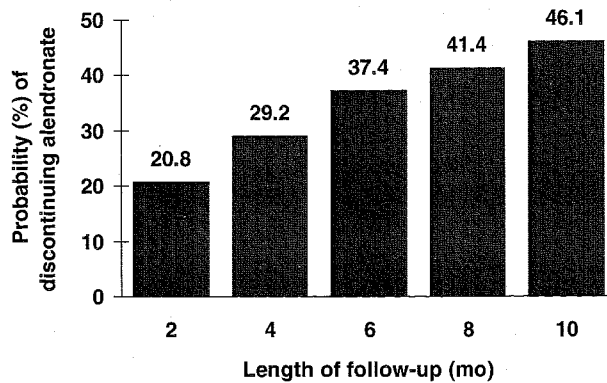


Table 1. Characteristics of 812 Women Receiving Alendronate and a Subset of 100 Women Who Had Acid-Related Upper Gastrointestinal Disorder (ARD) During Exposure to Alendronate*

Characteristic	No. (%) of subjects in entire cohort	No. of subjects		Relative risk of ARD (95% CI)
		with ARD	without ARD	
Used medications concomitantly with:				
NSAIDs or within 6 months before starting alendronate	276 (34)	45	231	1.7 (1.1,2.6)
Any oral glucocorticoid	159 (20)	23	136	1.2 (0.7,2.0)
NSAID or oral glucocorticoid	372 (46)	59	313	1.8 (1.2,2.7)
Failure to follow one or more dosing instructions:				
Any	453 (56)	68	385	0.6 (0.4,0.9)
Affecting safety	110 (14)	20	90	0.7 (0.4,1.2)
Altering absorption	420 (52)	58	362	0.8 (0.5,1.2)
Prior ARD diagnosis within 6 months before starting alendronate	78 (10)	21	57	3.1 (1.8,5.3)

NSAID = nonsteroidal anti-inflammatory drug
*CI indicates confidence interval

and hospital discharge diagnoses. From another database, we determined the total number of women who used the health plan during the same period, and we used that number in calculating ARD incidence rates.

Measurement of Alendronate Exposure Duration

Beginning after the initial prescription for alendronate was filled, we allowed an interval of 60 days between the time the previous supply of pills would have been exhausted and the time of each refill; any larger interval was considered a discontinuation. If treatment was stopped, we set the end of exposure at that time and assumed that half the number of pills in the prior prescription had been consumed.

Outcome Measures

For each of the 812 women, we searched for ARD diagnosed within 6 months before starting alendronate and while receiving alendronate. All ARD diagnoses from the outpatient clinic visit and hospitalization databases were obtained. If a hospital admission and outpatient visit were recorded on the same day, we used the admission diagnosis; if dyspepsia, nausea, or abdominal pain was recorded on the same day as a more specific ARD diagnosis, we used the more specific diagnosis.

Statistical Analysis

Logistic regression was used to test the statistical significance of potential variables for predicting diagnosis of ARD. We used Poisson regression to compare rates of ARD events among alendronate users and among the overall health plan population. All analyses were performed using SAS software (Cary, NC).⁷

... RESULTS ...

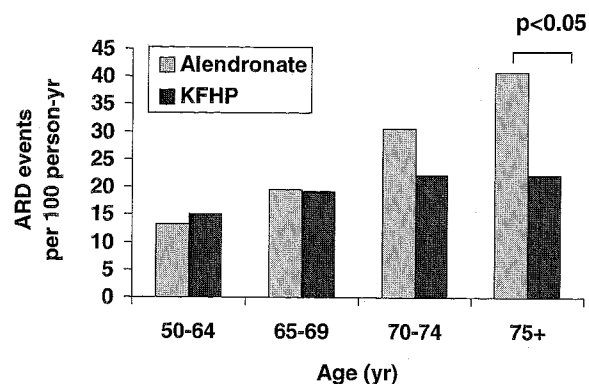
The mean (SD) age of the 812 alendronate users was 68.7 (11.7) years; the median age was 70 years. These women were followed a mean (SD) of 10 (6.8) months. The rate of alendronate discontinuation was linear over time, and by the end of follow-up, 46.1% of the women had discontinued alendronate (Figure 1). During the follow-up, 100 (12.3%) of the alendronate users received medical care for 135 ARD events, of which 19 (14%) prompted hospital admission and 116 (86%) prompted outpatient visits. ARD was diagnosed at a rate of 28.5 events per 100 person-years. ARD episodes showed a trend toward higher rates with increasing age of patients.

Alendronate users aged 70 years or older were 1.5 times more likely [95% confidence interval (CI) 1.0-2.3, *P* = 0.07] to have an ARD than alendronate users younger than 70 years. Use of NSAIDs was associated with statistically significant elevation of ARD risk: compared with nonusers of NSAIDs, relative risk (RR) was 1.7 (95% CI 1.1-2.6) (Table 1). We found a nonsignificant trend toward higher rates of ARD among users of oral glucocorticoid drugs: compared with nonusers of glucocorticoids, RR was 1.2 (95% CI 0.7-2.0).

Among 362,109 female health plan members aged 50 years or older, the overall rate of ARD diagnosis was 17.6 events per 100 person-years. A linear trend toward higher ARD rates was seen with increasing age: among women younger than 65 years, the rate was 15.1 events per 100 person-years; among women aged 65 through 69 years, 19.2 events per 100 person-years; for women aged 70 through 74 years, 22.1 events per 100 person-years; and for women 75 years or older, 22.2 events per 100 person-years. Compared with women in the general health plan population, users of alendronate had 1.6 times as many ARD events (95% CI 1.1-2.3). Risk was increased most among older women: alendronate users older than 70 years had 1.7 times more ARD events than nonusers who were of similar age (95% CI 1.2-2.3) (Figure 2).

The risk of having ARD during alendronate use was strongly associated with having a prior ARD diagnosis (RR 3.0, 95% CI 1.9-4.9 for prior ARD versus no prior ARD). Among the 734 women who had no prior ARD diagnosis, 10.8% received care for an ARD dur-

Figure 2. Incidence Rates by Age (per 100 Person-Years) for ARD Events Among 812 Women Using Alendronate Compared with Reference Group of 362,109 Women in Same Health Plan



ing follow-up, and the rate of ARD events was 23.8 events per 100 person-years. Among the 78 women who received care for ARD before starting alendronate, 26.9% received care for an ARD during follow-up and had 70.7 ARD events per 100 person-years.

Figure 3 shows ARD rates among women using alendronate and those in the general health plan population after excluding women who had ARD events or who used ARD drugs before the observation period. Rate ratio for these groups was 1.6 (95% CI 1.0-2.5). Here, too, age-related risk of ARD was seen in alendronate users compared with women in the general health plan population: the rate ratio (alendronate users versus nonusers) for new ARD events among women aged 70 years or older versus younger women was 1.8 (95% CI 1.2-2.6); the rate ratio for women aged 75 years or older versus younger women was 2.1 (95% CI 1.4-3.0).

In 41.3% of cases, alendronate was prescribed by endocrinologists or rheumatologists, specialists likely to be knowledgeable about alendronate use. ARD risk was not associated with prescriber type (RR 0.9, 95% CI 0.6-1.5, for endocrinologists or rheumatologists versus not). Women adhering to all safety dosing instructions had similar rates of ARD (32.7%) to those who failed to comply with one or more of these instructions (33.0%). Rates of ARD events decreased over time: the rate was 26.6 events per 100 person-years during the first 3 months of alendronate

use and declined to 14.4 events per 100 person-years at 6 months, 15.9 events per 100 person-years at 9 months, and 3.8 events per 100 person-years at one year.

... DISCUSSION ...

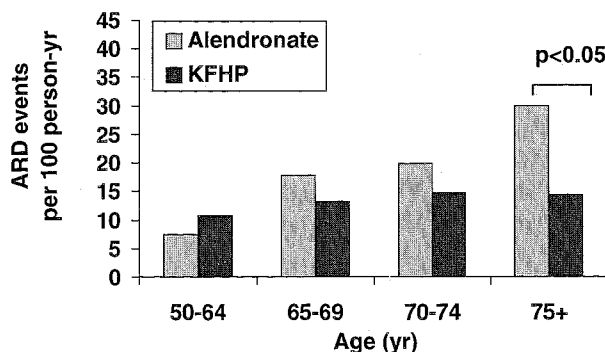
Extending our study of 812 women who received alendronate treatment for osteoporosis, we found that 1 in 8 received treatment for ARD during a mean 10 months after starting the drug. Most of these treatment events occurred in an outpatient setting. Advanced age, prior diagnosis of ARD, and use of NSAIDs were risk factors associated with significantly elevated rates of ARD events in this population. Failure to adhere to patient safety instructions did not affect the risk of alendronate-associated ARD.

Patients who have osteoporosis and take NSAIDs pose a challenge to clinicians. Chronic use of NSAIDs has for some time been known to irritate gastrointestinal mucosa and lead to gastrointestinal toxicity in some patients.^{8,9} The administration in rodents of combined alendronate and NSAID, compared with either agent alone, produced more frequent and larger gastric lesions, showed more histologic evidence of gastric damage, and slowed healing of gastric ulcers.¹⁰ In practice, a substantial proportion of elderly women may be expected to take NSAIDs. In our study, more than 1 in 3 alendronate users also took NSAIDs, and these women showed a 70% higher risk of ARD compared with those not taking NSAIDs.

The high rate of alendronate discontinuation in our study is consistent with many reports showing poor compliance with other long-term drug treatments for various conditions.¹¹ Our prior study¹ observed patients for a mean 4.4 months; the present study provided follow-up for a mean 10 months. The additional follow-up period suggested a linear trend in discontinuation (approximately 2.5% per month). The previous study¹ also showed that most women discontinuing alendronate reported gastrointestinal intolerance as the main reason for this discontinuation. Our current study suggests that ARD events recur among alendronate users, making it difficult or impossible for patients to comply with this treatment.

Elderly women are most frequently diagnosed with osteoporosis and thus are

Figure 3. Incidence Rates by Age (per 100 Person-Years) of ARD Events Among 812 Women Using Alendronate Compared with Reference Group of 326,768 Women in Same Health Plan and Excluding Women Who Had ARD Events or Who Used ARD Drugs Within 6 Months Before Follow-Up



also most likely to receive aggressive treatment to restore bone density and reduce fracture risk. Unfortunately, elderly women also have the highest prevalence of ARD and the highest use of drugs that can cause upper gastrointestinal irritation.⁵ When we analyzed the rate of ARD events in the reference group of female health plan members of similar age, we found (not unexpectedly) that as age increases, so does frequency of ARD. However, the same effect was more pronounced in the alendronate group. The higher rate of ARD events observed in the early months after starting alendronate and the progressively lower rates observed after 6 to 12 months support the hypothesis that alendronate intolerance markedly increases the frequency of ARD events leading to medical care. This effect is probably temporary, because patients who suffer new gastrointestinal side effects are likely to discontinue the drug.

The true risk for ARD associated with alendronate use might be higher or lower than the approximate twofold increase in risk that we observed. If osteoporosis could itself be a risk factor for ARD, then the risk attributable to alendronate would be lower. Conversely, if women receiving alendronate are less likely to have ARD because physicians either heed the warnings regarding its prescription or avoid prescribing it to frail women already receiving multiple medications, then the risk would be higher.

Ideally, a randomized clinical trial that does not exclude women at high risk for ARD could define the risk of ARD associated with alendronate. Mounting such a trial would pose both practical and ethical problems, however. An alternative plan would be to compare the rate of ARD among women diagnosed with osteoporosis to whom alendronate is prescribed with the rate among women to whom it is not prescribed. However, the decision not to prescribe alendronate for a woman with osteoporosis could be based on factors such as existing gastrointestinal problems, other chronic diseases, or multiple medication use which could bias the study by including healthier women in the alendronate group.

Our study had several limitations. We did not confirm ARD diagnoses by review of medical records. However, Levin and coworkers⁵ found that diagnoses from the Outpatient Summary Clinical Record database reliably reflected the diagnosis recorded in the medical chart. In addition, we did not determine the exact timing of ARD symptoms relative to time of initiating alendronate. Some delay

might exist between onset of symptoms and the clinic visit; or ARD symptoms might be managed without a clinic visit (ie, either by using a telephone call or by writing a prescription). These possibilities could have also caused us to underestimate the burden of alendronate-associated gastrointestinal problems.

Expanding on our previous observations that 1 in 3 women using alendronate reported new gastrointestinal symptoms, we now report that 1 in 8 women taking alendronate seek medical care for ARD. The risk of upper gastrointestinal problems requiring medical care is especially high among certain subpopulations—women who have received care for an ARD in the recent past, women using NSAIDs, and women aged older than 70 years. Careful monitoring of these high-risk women is therefore warranted. With increased use of alendronate to treat osteoporosis, we project a marked increase in the overall burden on the healthcare system imposed by the additional care needed for treating alendronate-associated ARD.

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