Yonsei Medical Journal
Vol. 44, No. 6, pp. 961 - 967, 2003

Gastrointestinal Side Effect Profile Due to the Use of Alendronate in the Treatment of Osteoporosis

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The aim of our study was to evaluate the upper gastrointestinal (GI) tract side effect profile in 759 female patients that had taken alendronate (10 mg/day), for at least 6 months, for the treatment of osteoporosis, in relation to the safety of alendronate and the compliance of patients to its absorption rules.

This study was a multicentered retrospective, clinical, non-placebo controlled, study of 759 female subjects carried out at 26 centres in 6 different regions of Turkey.

The mean age of our patients was 62.6 ± 8.6, with 51.2%in the age range 60 to 69 years. 158 patients (20.8%) were considered to have upper GI tract complaints with nausea as the most often encountered symptom. Of the subjects with upper GI tract complaints, 20% reported discontinued drug use, and 30% reported the requirement of an additional drug in order to abolish their complaints. Approximately 537 (71%) of the patients stated they had been given written information about the administration of the drug, and at least 93 patients (12%) and 73 patients (18.4%) acknowledged non compliance with the safety and absorption rules, respectively. In our study, no significant difference was found between the adherence to the safety measures and upper GI tract complaints ($p>0.05$), but that upper GI tract complaints were higher in patients taking additional medication to alendronate ($p<0.05$).

Key Words: Osteoporosis, alendronate, gastrointestinal system, side effect profile

Received November 27, 2002
Accepted August 13, 2003

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INTRODUCTION

Alendronate, used for the treatment of osteoporosis, is a potent inhibitor of bone resorption, which shows its effect by suppressing the increased rate of bone turnover during the postmenopausal period.[1] Like other biphosphonates, alendronate has the potential to cause upper gastrointestinal (GI) tract irritation.[2,3] Varying degrees of upper GI tract intolerance to alendronate, have been reported in its clinical applications. Of these,

abdominal pain, nausea, gastroenteritis, dyspepsia and vomiting are the most frequently reported.[4] In clinical practice, alendronate rarely leads to oesophageal events during treatment.[3]

Ingestion of the drug, with a glass of water, without chewing and sucking, and the importance of remaining up right for 30 minutes have been emphasized for the reduction of upper GI tract irritation and to increase the safe use, by increasing the passage of the drug into the system. However, full comprehension of the degree to which the upper GI tract irritation is decreased by these measures remains unknown.[5]

Absorption of alendronate from the GI tract is very low (<1%) and the degree of absorption varies with the ingestion of food and drinks, except water, and the concomitant administration of other medications. With respect to the absorption, ingesting the drug with water only, not eating 2 hours prior to and 30 minutes after, ingestion of the drug and not taking other medications concomitantly are recommended.[6,7]

The aim of our study was to evaluate the upper GI tract side effect profile of alendronate, in female patients that had taken alendronate (10 mg/day), for at least for 6 months, for the treatment of osteoporosis, the safety of the drug and the data of patients, in relation to their degree of knowledge of the absorption rules and their compliance with these rules.

MATERIALS AND METHODS

The study design was based on the International Kaiser Study conducted by Ettinger B, et al.,[5]- was amulticentered, carried out at 26 centres in 6 different regions of Turkey.- on 2158 patients during 2000, by the completion of inquiry forms prepared by Osteoporosis Society. In this retrospective, clinical, non-placebo controlled, study, these forms were completed by the physician during control examinations and face to face interviews. The part of inquiry relating to the use of alendronate,- was completed for the patients that had taken alendronate (10 mg/day) continuously for at least for 6 months. The inclusion criteria were: women (aged less than 80) in the postmenopausal period, for at least 6 months, with a lumbar (L1-4) or proximal femur bone mineral density (BMD) below 2 SD of the average premenopausal mean BMD. The exclusion criteria were: disorders of bone mineralization, an active systemic disease, malignancy, history of major GI tract mucosal erosive disease, defined as significant GI tract bleeding requiring hospitalization, hiatus hernia and upper or lower GI tract surgery. The medical history of upper GI tract conditions that did not exclude a subject from study participation were peptic ulcers or reflux oesophageal events. Of the 2158 patients, 759 used alendronate for osteoporosis treatment, while of the remaining the 1399, 722 and 683 used calcitonin and vitamin D, respectively.

The main questions on the form included: upper GI tract side effects profile due to the use of alendronate, if the patient has been informed, or not, about the rules to follow in respect to the absorption and safety of the drug and the compliance of the patients to these rules. Information about the upper GI tract side effects profile were collected by asking the patients if they had had nausea, epigastric pain, retrosternal pain, and pain when they swallowed the drug, during the period of alendronate administration. They were asked if they had received any written information that the drug should be ingested with at least a glass of water, remain up-right for 30 minutes after taking the drug, -not to eat or drink anything 2 hours prior to, and 30 minutes after, ingestion of the drug and not to take other medications concomitantly. The questions asked to evaluate the compliance to the drug were classified under two main titles; those that related to the safety and to the absorption of the drug.

- With regard to safety;
  You should take the medication with at least one big glass of water.
  You should stay in an up-right position for 30 minutes after the ingestion of the drug.
  You should not take the drug by chewing or sucking.
- With regard to absorption;
  You should be in a fasting state for 2 hours prior to taking the drug.
  You should not eat anything for 30 minutes after the ingestion of the drug.

You should not take the drug with drinks other than water.

You should not take the drug concomitantly with other medications.

SPSS (Statistical Package for Social Sciences Version 10, SPSS Inc., Chicago, IL, USA; Software-package) program was used to analyse the data of our study. Comparison of the results was made using Pearson chi-squared tests for unpaired observations. Results were considered significant when $p<0.05$.

RESULTS

The mean age of the study subjects was 62.6 ± 8.6, although 51.2% were in the age range 60 to 69 years (Table 1). The rate of subjects considered as having an upper GI tract complaint due to alendronate use was 20.8%, with the first sign being nausea, with a rate of 37.9%, followed by epigastric pain, with a rate of 35.1%. Of these patients, 20.2% had to discontinue the drug administration and 29.7% required an additional medication in order to abolish these complaints (Table 2). The most common side effects during alendronate use related to the upper GI tract, but other side effects included, diffuse bone and joint pain in 3 patients and skin disruption in a further 2.

There were 70 and 72% of patients that had received written information on the safety and absorption rules on the use of the drug (Table 3). Of these, 93 (12%) stated non compliance with at least one of the safety rules, and 73 (18.4%) with one of the absorption rules, during the drug utilisation (Table 4). There were no statistical differences between the upper GI tract complaints and the safety measures ($p>0.05$) (Table 5). The

Table 1. Age Distribution in the Alendronate Treatment Group

Age group (years)	Number of patients	%
40 years or less	8	1.1
40 - 49	27	3.5
50 - 59	225	29.6
60 - 69	389	51.2
70 - 79	99	13.1
80 years or more	11	1.4
Total	759	100

Table 2. Measures Taken by Subjects Who are Considered to Have Upper GI Tract Complaints Due to Alendronate Use

Patients having complaints	Number of patients	%
Yes	158	20.8 (100)*
Subjects discontinuing the drug	32	4.2 (20.2)
Subjects changing the administration	9	1.1 (5.6)
Subjects taking additional medication to alleviate the complaint?	47	6.2 (29.7)
Other measures	7	0.9 (4.4)
No	601	79.2
Total	759	100

*Values in parenthesis indicate the percent of the measures taken by the subjects having complaints.

Table 3. Patients Receiving Additional Written Information about the Safety and Absorption of the Drug

Information	Is information given?			
	Yes	%	No	%
- With regard to safety;				
You should take the medication with at least one glass of water	537	71	222	29
You should stay in an up-right position for 30 minutes after the ingestion of the drug	545	72	214	28
- With regard to absorption;				
You should be in fasting state within 2 hours before taking the drug	546	72	213	28
You should not eat anything within 30 minutes after the ingestion of the drug	544	72	215	28

Table 4. Patients Compliance to Safety and Absorption Rules

Rules to be followed	Patients compliance			
	Yes	%	No	%
- With regard to safety;				
Subjects taking at least with 1 glass of water	693	91	66	9
Subjects remaining in a up-right position for 30 minutes after the ingestion of the drug	666	88	93	12
Subjects taking the drug by chewing or sucking	24	3.2	735	96.8
- With regard to absorption;				
Subjects fasted within 2 hours before taking the drug	682	90	77	10
Subjects fasted within 30 minutes after taking the drug	671	88.4	88	11.6
Subjects not taking the drug with any drinks, except water	693	91	31	4
Subjects not taking alendronate concomitantly with other drugs	322	81.6	73	18.4

upper GI tract complaints were found to be significantly higher in the patients taking an additional drug (antacid, proton pump inhibitors and H_2 receptor blockers), than in those taking alendronate, alone ($p<0.05$) (Table 6).

DISCUSSION

The most common side effects during alendronate use were related with the upper GI tract, and varying rates of incidences reported. In the Fosamax International Trial Study Group (FOSIT), a study comprised of an extensive and long-term follow up, and in the Fracture Intervention Trial (FIT), these rates were 21.3 and 47.5%, respectively,[4,8] whereas 20.8% of our patients taking alendronate were observed to have upper GI tract complaints. The high extent of upper GI tract complaints in the general population, particularly the elderly, is a condition to be considered with caution. Continuous use of alendronate showed higher incidences of adverse events, particularly within older subgroups.[9] Another study suggests many upper GI tract adverse experiences reported during therapy with alendronate, which may reflect a high background incidence of upper GI tract complaints, with an increased sensitivity to detection of such complaints, rather than a causal relationship to the therapy.[10] Other studies have

Table 5. Comparison of the Upper GI Tract Complaints and Safety Measures

Safety measures	Upper GI tract complaint		
	Yes	No	*p*
- Subjects taking with at least 1 glass of water			
Yes	150	543	
No	8	58	> 0.05
- Subjects remaining in an up-right position for 30 minutes after the ingestion of the drug			
Yes	138	528	
No	20	73	> 0.05
- Subjects taking the drug by chewing or sucking			
Yes	2	22	
No	156	579	> 0.05

Table 6. Relation between Drug Administration and Upper GI Tract Complaints

Administration	Additional drug upper GI tract complaints (%)		
	Yes	No	Total
Yes	98 (24.8)	297 (75.2)	395 (100)
No	60 (16.5)	304 (83.5)	364 (100)
Total	158 (20.8)	601 (79.2)	759 (100)

Pearson Chi-Square: 7.86.
$p<0.05$.

shown alendronate use not to be associated with a significant increase in upper GI tract events among women suggested to have an increased risk for these events (those aged > or =75 years with previous upper GI tract disease or using nonsteroidal anti-inflammatory drugs-NSAID). In older women, upper GI tract complaints, particularly dyspepsia and abdominal pain, were common, but alendronate treatment was not associated with an increased incidence, even in the high-risk subgroups.[11,12] The risk of an adverse upper GI tract complaint increases with concurrent NSAID therapy, but the incidences were observed no more than with concurrent placebo and NSAID therapies. Also, the risk of adverse GI tract events can be decreased by following the dosing instructions.[13] A study on this issue, showed that 20% of the population have some complaints that were independent of the use of placebo or alendronate.[14] Therefore, the reported upper GI tract complaints from patients prescribed alendronate, as yet, have not been directly associated to the drug use. There have been different results reported on the complaints during alendronate treatment, comments on this issue and in the patients selection criteria. The rates of patients discontinuing therapy due to side effects have varied from 4 to 30% in different studies.[4,5,13,15] The higher rate in retrospective trials, exceeding those in prospective studies, merits attention, but it is our assumption that the study method, patient and physician factors have an influence on these differences. The discontinuation rate in our study was 4.2%, which was generally lower than in other retrospective trials. A possible explanation for of this lower rate may

be that a greater number of the patients included in our study were closely monitored at osteoporosis outpatient clinics. Our patients were carefully selected according to indication and contraindication. Hence, the administration of an additional medication, to alleviate the complaints in 47 (29.7%) of the patients with upper GI tract complaints, shows the importance of physician recommendation in closely monitored patients. Despite the conflicting view that alendronate administration causes more frequent upper GI tract complaints, trials relating to this subject, including FOSIT and FIT, have demonstrated no significant difference between the alendronate and placebo groups.[4,8,16-19] In our study there was no comparison on the side effect frequencies with a placebo group, which is a potential area for criticism. The degree of efficacy of the recommended safety measures to reduce the upper GI tract irritation caused by the use of alendronate ,is not well understood. Ettinger, et al. found no statistical difference between compliance and non compliance with the safety rules in regard to the upper GI tract complaints.[5] In our study, 93 (12%) of patients admitted non compliance in staying up right for 30 minutes, and 73 (18.4%) with the rule for not taking concomitant medication, a safety and an absorption rule, respectively (Table 4). It was important that fewer of the patients showed non compliance with the rules, if they had not received written information, compared to those that had. It was noteworthy that a smaller number of patients than patients who had received written instructions concerning safety and absorption showed non compliance. This result suggested that patients that did not receive written information, had been verbally informed about the safety and absorption measures. This also shows that being told verbally is more effective than being informed in writing. These results suggest that a greater number of patients than was indicated in Table 5 were in some way informed about safety and absorption rules of the drug. Some patients were not accustomed to reading labels on medication. Therefore verbal instructions seem to be very effective. These results suggest that the patients may have been better informed than indicated in Table 5. A study on this subject, reported that the rate of the subjects not complying with any one of the safety rules was 13.5%.[5] In our study, no significant difference was observed between the compliant and non compliant groups when the association between safety measures and upper GI tract complaints were evaluated (Table 5).

Of the patients in our study, 395 (52%) reported use of an additional medication within the last year. Of the patients taking specific GI medication, 153 (38.8%) received antacid, 92 (23.2%) proton pump inhibitors, 84 (21.3%) H_2 receptor blockers and 66 (16.7%) antacid, with proton pump inhibitors, or H_2 receptor blockers, also. No significant difference between the compliant and non compliant groups was observed according to adverse upper GI tract events. The rate of upper GI tract complaints of the patients reporting concomitant medication use during alendronate administration, was 98 (24.8%), while this was 60 (16.5%) for those not taking an additional medication (Table 6). When the relation between the use of a concomitant medication, within last year were compared with upper GI tract complaints, significantly higher upper GI tract complaints were found among those taking concomitant medications.

In conclusion, the use of alendronate (10 mg/day) for at least 6 months, was observed not to cause any increase in upper GI tract complaints compared to the normal population. Patients should receive both verbal and written instructions. There was no significant difference between the patients complying or not complying with the safety measures in relation to upper GI tract complaints. However, because of the significantly higher rate of upper GI tract complaints in subjects with a history of medication use the choice of medication when treating osteoporosis in these patients should be performed with more caution.

REFERENCES

1. Rodan GA, Fleisch HA. Bisphosphonates; Mechanisms of action. J Clin Invest 1996;97:2692-6.
2. Peter CP, Handt LK, Smith SM. Esophageal irritation due to alendronate sodium tablets: Possible mechanisms. Dig Dis Sci 1998;43:1998-2002.
3. Sharpe M, Noble S, Spencer CM. Alendronate: an update of its use in osteoporosis. Drugs 2001;61:999-1039.

4. Pols HA, Felsenberg D, Hanley DA, Stepan J, Munoz-Torres M, Wilkin TJ, et al. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Fosamax International Study Group. Osteoporos Int 1999;9:461-8.
5. Ettinger B, Presmann A, Schein J, Chan J, Silver P, Connoly N. Alendronate use among 812 women: Prevalence of gastrointestinal complaints, noncomplaints with patients instructions, and discontinuation. JMCP 1998;4:488-92.
6. Gertz BJ, Holland SD, Kline WF, Matuszewski BK, Freeman A, Quan H, et al. Studies of the oral bioavailability of alendronate. Clin Pharmacol Ther 1995; 58:288-98.
7. Gertz BJ, Holland SD, Kline WF, Matuszewski BK, Porras AG. Clinical pharmacology of alendronate sodium. Osteoporos Int 1993;3:13-6.
8. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the fracture intervention study. JAMA 1998;280: 2077-82.
9. Watts N, Freedholm D, Daifotis A. The clinical tolerability profile of alendronate. Int J Clin Pract Suppl 1999;101:51-61.
10. Sahota O, Fowler I, Blackwell PJ, Lawson N, Cawte SA, San P, et al. A comparison of continuous alendronate, cyclical alendronate and cyclical etidronate with calcitriol in the treatment of postmenopausal vertebral osteoporosis: a randomized controlled trial. Osteoporos Int 2000;11:959-66.
11. Bauer DC, Black D, Ensrud K, Thompson D, Hochberg M, Nevitt M, et al. Upper gastrointestinal tract safety profile of alendronate: the fracture intervention trial. Arch Intern Med 2000;160:517-25.
12. Baker DE. Alendronate and risedronate: what you need to know about their upper gastrointestinal tract toxicity. Rev Gastroenterol Disord 2002;2:20-33.
13. Miller PD, Woodson G, Licata AA, Ettinger MP, Mako B, Smith ME, et al. Rechallenge of patients who had discontinued alendronate therapy because of upper gastrointestinal symptoms. Clin Ther 2000;22:1433-42.
14. Talley NJ, Weaver AL, Zinsmeister AR, Melton LJ 3rd. Onset and disappearance of gastrointestinal disorders. Am J Epidemiol 1992;136:165-71.
15. Tonino RP, Meunier PJ, Emkey R, Rodriguez-Portales JA, Menkes CJ, Wasnich RD, et al. Skeletal benefits of alendronate: 7 year treatment of postmenopausal osteoporotic women. Phase III osteoporosis treatment study group. J Clin Endocrinol Metab 2000;85:3109-15.
16. Liberman UA, Weiss SR, Broll J. Effect of oral alendronate on bone mineral density and incidence of fractures in postmenopausal osteoporosis. N Engl J Med 1995;333:1437-43.
17. Chesnut CH III, McClung MR, Ensrud KE. Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodelling. Am J Med 1995;99:144-52.
18. Adami S, Passeri M, Ortolani S, Broggini M, Carratelli L, Caruso I, et al. Effects of oral alendronate and intranasal salmon calcitonin on bone mass and biochemical markers of bone turnover in postmenopausal woman with osteoporosis. Bone 1995;17:383-90.
19. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1996;348:1535-41.