

ORIGINAL ARTICLE

Comparative effects of treatment with etidronate and alendronate on bone resorption, back pain, and activities of daily living in elderly women with vertebral fractures

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(Received for publication on May 2, 2003)

Abstract. The purpose of the present study was to compare the effects of treatment with etidronate and alendronate on bone resorption, back pain, and activities of daily living (ADL) in elderly women with vertebral fractures. Fifty elderly women, 63–84 years of age, with back pain due to osteoporotic vertebral fractures were randomly divided into two groups with 25 patients in each group: the cyclical etidronate treatment group (200 mg/day for 2 weeks per 3 months) and the alendronate treatment group (5 mg/day). The level of urinary cross-linked N-terminal telopeptides of type I collagen (NTx) measured by an enzyme-linked immunosorbent assay, back pain evaluated with the face scale score, and the ADL score (disability) determined with a questionnaire were assessed before and 3 and 6 months after the start of treatment. No significant differences in these parameters were found between the two groups before the treatment. The urinary NTx level, the face scale score, and the ADL score decreased significantly in both groups. Although the reduction in the urinary NTx level was significantly greater in the alendronate group than in the etidronate group, the reduction in the face scale score was transiently significantly greater in the etidronate group than in the alendronate group. However, changes in the ADL score did not significantly differ between the two groups. The present study showed that although back pain was reduced and ADL was improved in both treatment groups of elderly women with vertebral fractures, the mechanism for the reduction in back pain differs to some extent between the two treatment groups. A double-blind placebo-controlled study is needed to confirm the therapeutic effects of these agents on back pain and deterioration of ADL. (*Keio J Med* 52 (4): 230–235, December 2003)

Key words: bone resorption, back pain, urinary cross-linked N-terminal telopeptides of type I collagen (NTx), bisphosphonate

Introduction

Vertebral fractures occur in the natural history of osteoporosis and are associated with back pain, immobility, and disability. Pain control is a crucial factor determining the activities of daily living (ADL) and subsequently the quality of life (QOL) in elderly patients. Since back pain accompanied by osteoporotic vertebral fracture appears to be linked to increased

bone resorption, drugs affecting bone metabolism such as bisphosphonates which are anti-resorptive agents may be useful for pain control in patients with vertebral fractures.

Etidronate and alendronate are bisphosphonates commercially available for osteoporosis in Japan. The efficacy of treatment with cyclical etidronate (200 mg/day for 2 weeks per 3 months) and alendronate (5 mg/day) to increase bone mineral density and reduce the

incidence of osteoporotic fractures in Japanese patients with osteoporosis has been clearly demonstrated.^{1–3} However, very few studies have reported their therapeutic effects on back pain and/or deterioration of ADL in patients with vertebral fractures.

It has been reported that women randomized to alendronate treatment had a significantly lower risk of outcomes that are important to patients – number of days of bed rest and limited activity due to back pain.⁴ The results of this report suggest that alendronate treatment in elderly osteoporotic women is efficacious for preventing back pain and subsequent deterioration of ADL (preventative effects). However, the therapeutic effect of alendronate treatment and the preventative and therapeutic effect of etidronate treatment on back pain and deterioration of ADL in patients with vertebral fractures have rarely been reported. In fact, it may be difficult ethically to perform double-blind placebo-controlled studies in patients with vertebral fractures in order to assess the therapeutic effect of some treatments on back pain. Recently, we reported that etidronate treatment transiently reduced metastatic cancer bone pain in patients with painful bone metastases from primary cancer sites, by decreasing abnormally raised bone resorption.⁵ We surmise that both treatment with etidronate and alendronate may have the potential to reduce back pain and improve ADL in patients with vertebral fractures, helping to improve their QOL. The aims of the present prospective randomized open-label study were to determine whether treatment with etidronate and alendronate could reduce back pain and improve ADL in patients with vertebral fractures, and to compare their therapeutic effects on bone resorption, back pain, and ADL.

Subjects and Methods

Subjects

Fifty elderly women, 63–84 years of age, with back pain associated with osteoporotic vertebral fractures were recruited at our hospitals between October and December 2001. Vertebral fracture was defined as described below. They were randomly divided into two treatment groups with 25 patients in each group: the cyclical etidronate treatment group (200 mg/day for 2 weeks per 3 months) and the alendronate treatment group (5 mg/day). These doses are recognized as effective for Japanese patients with osteoporosis. All subjects did not take medicine such as non-steroidal anti-inflammatory drugs to relieve back pain. All subjects were instructed to take 800 mg of calcium daily through food intake. All subjects completed the trial without any adverse effects. Table 1 shows the characteristics of the study subjects. Pre- and post-treatment examina-

Table 1 Characteristics of Study Subjects

	Etidronate group n = 25	Alendronate group n = 25
Age (years)	72.1 ± 1.2 (63–83)	75.0 ± 1.0 (65–84)
Height (cm)	149.4 ± 1.2 (140–170)	147.9 ± 1.5 (135–165)
Body weight (kg)	48.3 ± 1.6 (31–68)	48.5 ± 1.8 (34–72)
BMI (kg/m ²)	21.6 ± 0.6 (14.7–28.3)	22.1 ± 0.6 (16.9–29.6)
Number of prevalent vertebral fractures	3.7 ± 0.6 (1–8)	3.1 ± 0.5 (1–8)
Serum calcium (mg/dl)	9.5 ± 0.1 (8.9–10.5)	9.4 ± 0.1 (8.8–9.9)
Serum phosphorus (mg/dl)	3.4 ± 0. (2.8–3.8)	3.3 ± 0.1 (2.9–4.1)

Data are expressed as mean ± SE. Unpaired t-test was used to compare the data between the two groups. Numbers in parenthesis are ranges. No significant differences in any baseline characteristics were found between the two groups.

tions included medical history, physical examination, and plain X-ray examination of the thoracic and lumbar spine. A blood sample was also obtained before the start of treatment, and serum calcium and phosphorus levels were measured with standard laboratory techniques. The diagnosis of osteoporosis was made according to the Japanese criteria of primary osteoporosis as described below. None of the subjects suffered from any metabolic bone disease, and none had a history of hormone (estrogen) replacement therapy or had ever taken medication that affects bone metabolism prior to the present study. The level of urinary cross-linked N-terminal telopeptides of type I collagen (NTx) was measured, and the face scale score as an index of back pain was determined before and 3 and 6 months after the start of treatment as described below. The ADL score (disability) was also assessed with a questionnaire⁶ before and 3 and 6 months after the start of treatment. Lateral X-ray films of the thoracic and lumbar spine were obtained before and 6 months after the start of treatment to assess vertebral fractures. Informed consent was obtained from all participants.

Assessment of vertebral fractures

Plain lateral X-ray films of the thoracic and lumbar spine were obtained to find evidence of vertebral fractures. Vertebral fractures were defined according to the vertebral height obtained from lateral X-ray films based on the Japanese criteria.^{7,8} Briefly, the vertebral height was measured at the anterior (A), center (C), and posterior (P) part of the vertebral body, and the presence of vertebral fractures was confirmed when (1) more than a 20% reduction of vertebral height (A, C, and P) compared with the neighboring vertebrae was observed; (2) C/A or C/P was less than 0.8; or (3) A/P was less

than 0.75. The assessment of vertebral fractures was performed for the T4–L4 spine in the present study.

Diagnosis of osteoporosis

The diagnosis of osteoporosis was made from lateral X-ray films of the spine on the basis of the Japanese diagnostic criteria of primary osteoporosis.^{7,8} Evaluation of bone mass can be made from lateral X-ray films of the spine when a vertebral fracture and/or lumbar spondylosis is present. Briefly, there are three grades according to the appearance of the longitudinal trabeculae on lateral X-ray films of the spine: Grade I: the longitudinal trabeculae are prominent, Grade II: the longitudinal trabeculae are coarse, Grade III: the longitudinal trabeculae are unclear. When a nontraumatic vertebral fracture is present on lateral X-ray films of the spine, Grade I or more severe radiographic osteopenia should be diagnosed as osteoporosis. When a nontraumatic vertebral fracture is not present on lateral X-ray films of the spine, Grade II or more severe radiographic osteopenia should be diagnosed as osteoporosis.

Measurement of urinary NTx level

Urine samples were collected in the morning after an overnight fast, and stored at -70°C until assayed. Urinary NTx level (nmol BCE/mmol Cr) was estimated using an enzyme-linked immunosorbent assay (ELISA, Osteomark, Ostex International, Seattle, WA) with a monoclonal antibody against the N-telopeptide to the helix intermolecular cross-linking domain of type I collagen. All samples were measured in duplicate, and the samples were analyzed in the same assay to eliminate inter-assay variations. The assay sensitivity was 20 nM bone collagen equivalents. The intra-assay coefficient of variation of 5 measurements was less than 7%.

Evaluation of back pain

Back pain was evaluated quantitatively by assessing the mood of patients according to the face scale. The face scale contains ten drawings of a single face, arranged in serial order by rows, with each face depicting a slightly different mood. Subtle changes in the eyes, eyebrows, and mouth are used to represent slightly different levels of mood. They are arranged in decreasing order of mood and numbered from 1–10, with 1 representing the most positive mood and 10 representing the most negative mood. As the examiner pointed to the faces, the following instructions were given to each patient: “The faces below go from painless at the top to very painful at the bottom. Point to the face that best shows the way you are currently experiencing back pain.” Thus, facial expression is used as an indicator of back pain. The validity and reliability of the face scale

have been demonstrated,⁹ although pain is a subjective symptom that is relatively difficult to evaluate.

Statistical analysis

Data are expressed as mean \pm standard error (SE). Data comparisons between the two groups were performed by unpaired t-test. The significance of longitudinal changes in the urinary NTx levels, the face scale scores, and the ADL scores was also determined by one-way analysis of variance (ANOVA) with repeated measurements. Furthermore, longitudinal changes in these three parameters were compared between the two groups by two-way ANOVA with repeated measurements. The correlations among the baseline urinary NTx level, the face scale score, the ADL score, and the number of prevalent vertebral fractures in all subjects were examined by single regression analysis. The correlations among percent changes in the urinary NTx

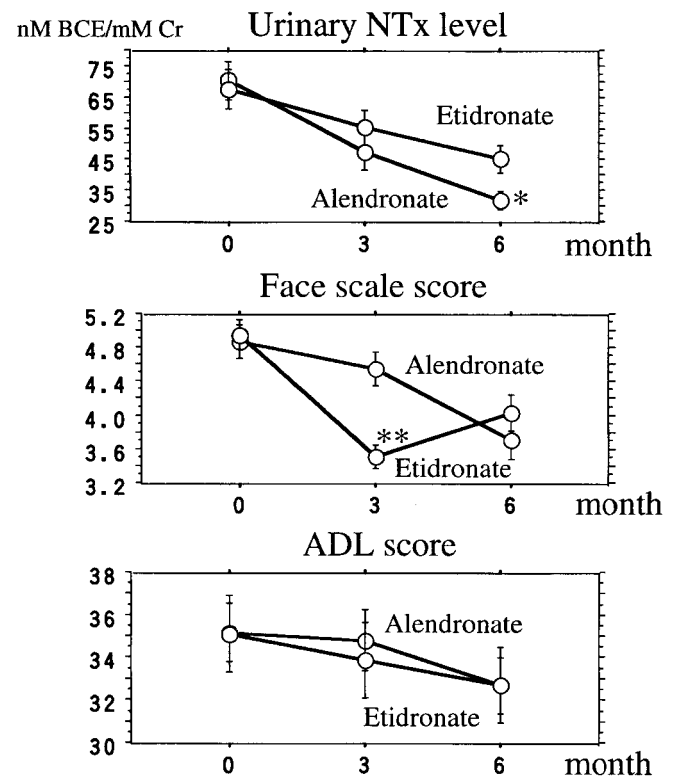


Fig. 1 Changes in the urinary NTx level, face scale score, and ADL score. One-way ANOVA with repeated measurements showed that the urinary NTx level, face scale score, and ADL score were significantly decreased in both groups (all $P < 0.0001$). Two-way ANOVA with repeated measurements showed that longitudinal changes in the urinary NTx level and face scale score significantly differed between the two groups ($P < 0.05$ and $P < 0.0001$, respectively), while longitudinal changes in the ADL score did not significantly differ between the two groups. * $P < 0.01$ vs etidronate group, ** $P < 0.001$ vs alendronate group by unpaired t-test. NTx: cross-linked N-terminal telopeptides of type I collagen, ADL: activities of daily living.

level, the face scale score, and the ADL score in each group were also examined by single regression analysis. All statistical analyses were performed using the Stat View-J5.0 program on a Macintosh computer. A significance level of $P < 0.05$ was used for all comparisons.

Results

Changes in the urinary NTx level, the face scale score, and the ADL score

The baseline urinary NTx level was 67.8 ± 31.1 nmol BCE/mmol Cr in the etidronate group and 65.8 ± 19.9 nmol BCE/mmol Cr in the alendronate group. The respective baseline face scale score was 5.0 ± 0.9 and 4.9 ± 1.0 , and the respective baseline ADL score was 35.2 ± 8.9 and 35.1 ± 7.0 . There were no significant differences in these baseline parameters between the two groups. Fig. 1 shows the changes in these parameters. One-way ANOVA with repeated measurements showed that the urinary NTx level, face scale score, and ADL score decreased significantly in both groups (all $P < 0.0001$). Two-way ANOVA with repeated measurements showed that longitudinal changes in the urinary NTx level and face scale score significantly differed between the two groups ($P < 0.05$ and $P < 0.0001$, respectively), while longitudinal changes in the ADL score did not significantly differ between the two groups. On the unpaired t-test, the urinary NTx level 6 months after the start of treatment was significantly lower in the alendronate group than in the etidronate group ($P < 0.01$), and the face scale score 3 months after the start of treatment was significantly lower in the etidronate group than in the alendronate group ($P < 0.001$).

Correlation among baseline number of prevalent vertebral fractures, urinary NTx level, face scale score, and ADL score in all subjects

Table 2 shows that a significant positive correlation was found between the baseline number of prevalent vertebral fractures and the urinary NTx level in all subjects ($r = 0.360$, $p < 0.05$), while no significant correlation was found between the baseline number of prevalent vertebral fractures and the face scale and ADL scores. A significant positive correlation was found between the baseline face scale and ADL scores in all subjects ($r = 0.252$, $p < 0.05$), while no significant correlation was found between the baseline urinary NTx level and the face scale and ADL scores.

Correlation among percent changes in the urinary NTx level, face scale score, and ADL score in each group

Table 3 shows that 3 months after the start of treatment, in both groups, no significant correlation was

Table 2 Correlation among Baseline Number of Prevalent Vertebral Fractures, Urinary NTx Level, Face Scale Score, and ADL Score in All Subjects

	Urinary NTx level	Face scale score	ADL score
Number of prevalent vertebral fractures	+0.360*	+0.114	+0.121
Urinary NTx		+0.103	+0.011
Face scale score			+0.252*

Data are r values. Single regression analysis was used to examine the correlation among the number of prevalent vertebral fractures, urinary NTx level, face scale score, and ADL score in all subjects. * $P < 0.05$

found among percent changes in the urinary NTx level, face scale score, and ADL score. Six months after the start of treatment, in the alendronate group, a significant positive correlation was found between percent decreases in the urinary NTx level and face scale score ($r = 0.356$, $p < 0.05$), while no significant correlation was found between percent changes in the ADL score and urinary NTx level and face scale. In the etidronate group, no significant correlation was found among percent changes in the urinary NTx level, face scale score, and ADL score.

Incident vertebral fractures

Six months after the start of treatment, three incident vertebral fractures (T7, T8, L4) were observed in a patient with a prevalent vertebral fracture (L3) in the etidronate group, while no incident vertebral fractures occurred in the alendronate group.

Discussion

The present study showed a significant positive correlation between the baseline face scale score and the

Table 3 Correlation among Percent Changes in Urinary NTx Level, Face Scale Score, and ADL Score in Each Group

	Etidronate group		Alendronate group	
	Face scale score	ADL score	Face scale score	ADL score
3 months				
Urinary NTx	+0.312	-0.173	+0.290	+0.307
Face scale score		-0.373		+0.259
6 months				
Urinary NTx	+0.240	+0.301	+0.356*	+0.081
Face scale score		+0.175		+0.012

Data are r values. Single regression analysis was used to examine the correlation among the percent changes in the urinary NTx level, face scale score, and ADL score by 3 and 6 months of treatment in each group. * $P < 0.05$

ADL score, suggesting that back pain is a significant factor affecting ADL in elderly women with vertebral fractures. This finding provides important information on measures to achieve improvement of deteriorated ADL and subsequent QOL in elderly people. The present study also showed a significant positive correlation between the baseline number of prevalent vertebral fractures and the urinary NTx level, suggesting that high bone turnover may be associated with a higher risk of vertebral fractures in patients with osteoporosis as previously reported.^{10,11} We believe that in elderly women with vertebral fractures who show higher levels of bone resorption (turnover) markers, bisphosphonate treatment may potentially reduce bone resorption and back (bone) pain, because non-traumatic painful vertebral fractures result from increased bone resorption.

Back pain was reduced and ADL was improved in both treatment groups of elderly women with vertebral fractures. Nevitt *et al.*⁴ have reported that long-term alendronate treatment has a significantly lower risk of patients having days of bed rest and limited activity due to back pain in elderly osteoporotic women, suggesting that alendronate treatment in elderly osteoporotic patients is efficacious not only for preventing incident vertebral fractures by suppressing bone resorption, but also for reducing the burden of activity limitation and bed disability caused by back pain. However, the therapeutic effects of alendronate treatment on back pain and deterioration of ADL in patients with vertebral fractures have rarely been reported. Agarwala *et al.*¹² reported that short-term alendronate treatment improves pain, disability, and standing and walking capacity in patients with avascular necrosis of the hip. The mechanism of the beneficial action of alendronate in avascular necrosis is speculated to be inhibition of the resorptive action of mature osteoclasts, an increase in the level of apoptosis of osteoclasts, and probably a decrease in apoptosis of osteoblasts and osteocytes. The main mechanism by which alendronate treatment prevents and/or reduces pain in patients with increased bone resorption seems primarily to be suppression of bone resorption.

The preventative and therapeutic effects of etidronate treatment on back pain and deterioration of ADL in patients with vertebral fractures have rarely been reported. In the etidronate treatment group of the present study, despite the reductions in the urinary NTx level and face scale score over 6 months, the percent decrease in urinary NTx level was not significantly correlated with the percent decrease in the face scale score. Thus, other mechanisms than suppression of bone resorption might contribute to the reduction in back pain. Recently, we reported that etidronate treatment transiently reduced metastatic cancer bone pain in patients with painful bone metastases from primary

cancer sites by decreasing abnormally raised bone resorption.⁵ Metastatic bone pain can be attributed to an indirect effect of osteoclast-mediated bone resorption, and the release of prostaglandins, bradykinin, substance P, and histamine.^{13,14} Available evidence suggests that etidronate decreases pain by suppressing the production of interleukin (IL)-6, IL-12, and prostaglandin E2.^{15,16} Thus, a possible explanation for the relief of metastatic cancer bone pain achieved by etidronate may be the combined effects of suppression of bone resorption and a reduction in the production of ILs and prostaglandin. Although alendronate treatment has also been reported to reduce the levels of cytokines such as IL-1, IL-6, and tumor necrosis factor (TNF)- α in patients with early rheumatoid arthritis,¹⁷ the pain relief effect of alendronate treatment remains uncertain. Because the reduction in urinary NTx levels was less in the etidronate treatment group than in the alendronate treatment group, the reduction in the production of ILs and prostaglandin in the etidronate treatment group might contribute more significantly to the reduction in back pain 3 months after the start of treatment. Further study is needed to confirm the effect of etidronate treatment on ILs and prostaglandin.

Although a significant positive correlation was found between the baseline face scale score and ADL score in all subjects, no significant correlation was found between the reductions in the face scale score and ADL score in both groups. This finding suggests that back pain can contribute the deterioration of ADL, but the relief of back pain does not always result in the improvement of ADL. Thus, mechanisms other than pain relief might contribute to the improvement of ADL. One possibility is that mental improvement resulting from precise diagnosis of osteoporosis, proper treatment for it, and pain relief might lead to the improvement of ADL, because there are many elderly women with osteoporosis who feel mental depression. Another possibility is that the patient might realize the importance of increasing physical activity in the treatment of osteoporosis, resulting in the improvement of ADL. However, further study is needed to confirm these views.

Because pain is a subjective symptom of patients, the major problem of the present study is that there were no placebo controls. First, in general, placebo effects tend to appear abruptly in the initial phase and earlier than true effects, and to be transient in nature. Therefore, whether a transient decline in the face scale score in the etidronate treatment group reflects a true drug effect is not known. A double-blind placebo-controlled study is needed to clarify this. Second, because the severe pain of vertebral fractures in some patients may be transient, resolving within a few weeks to a few months, whether a longitudinal decline in face scale score in the

etidronate and alendronate treatment groups reflects a true drug effect is not also known. However, the efficacy of bisphosphonates for bone pain in patients with bone resorption-related diseases has been demonstrated. Intravenous pamidronate seems to be a valuable treatment for back pain, as well as rehabilitating elderly patients suffering from chronic and refractory back pain due to osteoporotic vertebral fractures,¹⁸ and also reduces skeletal pain and biochemical markers of bone resorption in patients with skeletal metastases.^{19,20} Furthermore, risedronate decreases bone pain in patients with Paget's disease of bone.²¹ In the alendronate treatment group of the present study, the percent decrease in the urinary NTx level was significantly positively correlated with the percent decrease in the face scale score 6 months after the start of treatment. Thus, we believe that suppressed bone resorption might contribute to the relief of back pain at least in the alendronate treatment group of patients with vertebral fractures. However, a double-blind placebo-controlled study is needed to confirm the efficacy of treatment with etidronate and alendronate for back pain and deterioration of ADL.

In conclusion, the present study showed a reduction in back pain and improvement of ADL was seen in the etidronate and alendronate treatment groups of elderly women with vertebral fractures. Although the reduction in the urinary NTx level was greater in the alendronate treatment group than in the etidronate treatment group, the reduction in the face scale score was transiently greater in the etidronate treatment group than in the alendronate treatment group. However, changes in the ADL score were similar in the two treatment groups. Thus, the mechanism for the reduction in back pain differs somewhat between the two treatment groups. A double-blind placebo-controlled study is needed to confirm the therapeutic effects of these agents on back pain and deterioration of ADL.

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