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Effects of Oral Alendronate in Elderly Patients with Osteoporosis and Mild Primary Hyperparathyroidism

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ABSTRACT

In a large proportion of the patients with primary hyperparathyroidism (PHPT), a variable degree of osteopenia is the only relevant manifestation of the disease. Low bone mineral density (BMD) in patients with PHPT is an indication for surgical intervention because successful parathyroidectomy results in a dramatic increase in BMD. However, low BMD values are almost an invariable finding in elderly women with PHPT, who are often either unwilling or considered unfit for surgery. Bisphosphonates are capable of suppressing parathyroid hormone (PTH)–mediated bone resorption and are useful for the prevention and treatment of postmenopausal osteoporosis. In this pilot-controlled study, we investigated the effects of oral treatment with alendronate on BMD and biochemical markers of calcium and bone metabolism in elderly women presenting osteoporosis and mild PHPT. Twenty-six elderly patients aged 67–81 years were randomized for treatment with either oral 10 mg alendronate on alternate-day treatment or no treatment for 2 years. In the control untreated patients a slight significant decrease was observed for total body and femoral neck BMD, without significant changes in biochemical markers of calcium and bone metabolism during the 2 years of observation. Urine deoxypyridinoline (Dpyr) excretion significantly fell within the first month of treatment with alendronate, while serum markers of bone formation alkaline phosphatase and osteocalcin fell more gradually and the decrease became significant only after 3 months of treatment; thereafter all bone turnover markers remained consistently suppressed during alendronate treatment. After 2 years in this group we observed statistically significant increases in BMD at lumbar spine, total hip, and total body (+8.6 ± 3.0%, +4.8 ± 3.9%, and +1.2 ± 1.4% changes vs. baseline mean ± SD) versus both baseline and control patients. Serum calcium, serum phosphate, and urinary calcium excretion significantly decreased during the first 3–6 months but rose back to the baseline values afterward. Increase in serum PTH level was statistically significant during the first year of treatment. These preliminary results may make alendronate a candidate as a supportive therapy in patients with mild PHPT who are unwilling or are unsuitable for surgery, and for whom osteoporosis is a reason of concern. (J Bone Miner Res 2001;16:113–119)

Key words: primary hyperparathyroidism, alendronate, osteoporosis, bisphosphonates

INTRODUCTION

IN POSTMENOPAUSAL women osteoporosis and primary hyperparathyroidism (PHPT) are two common disorders. PHPT is associated with cortical osteopenia and some investigators have reported an increased risk for osteoporotic fractures.[1–3] Successful parathyroidectomy results in dramatic increases in both lumbar spine and femoral neck bone mineral density (BMD).[4–10] These recent findings tend to broaden the indications for surgery, and low BMD, in

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TABLE 1. BASELINE CLINICAL CHARACTERISTICS AND BMDS IN THE TWO PROSPECTIVE GROUPS AND IN THE RETROSPECTIVE SURGICALLY TREATED PATIENTS (MEAN AND SD)

Characteristics	*Alendronate group (n = 13)*	*Control group (n = 13)*	*Surgical group (n = 13)*
Age (years)	72 (5)	74 (4)	61 (4)
Time since menopause (years)	23 (7)	24 (8)	13 (6)
Body mass index (kg/m^2)	24.7 (3.5)	23.8 (3.2)	23.9 (2.6)
BMDs			
Femoral neck (g/cm^2)	0.577 (0.057)	0.554 (0.038)	
T score femoral neck (SD)	−3.2 (0.6)	−3.5 (0.4)	
Z score femoral neck (SD)	−0.7 (0.6)	−0.8 (0.5)	
Trochanter (g/cm^2)	0.459 (0.062)	0.440 (0.071)	
Ward triangle (g/cm^2)	0.390 (0.076)	0.377 (0.106)	
Total hip (g/cm^2)	0.607 (0.069)	0.566 (0.078)	
Lumbar spine (g/cm^2)	0.700 (0.090)	0.728 (0.070)	0.738 (0.093)
Total body (g/cm^2)	0.820 (0.062)	0.815 (0.098)	

patients with otherwise asymptomatic PHPT, has become an indication for surgical intervention.[11] Low BMD values are almost invariably found in elderly women with PHPT and in a large proportion of them osteopenia is the only relevant manifestation of the disease. However, a large proportion of these patients with mild PHPT have complex medical problems and are either unwilling or considered unfit for parathyroid surgery. This makes a medical approach oriented at the recovery and conservation of bone mass somewhat attractive. Hormone-replacement therapy (HRT) significantly increases BMD and reduces urinary calcium excretion and bone turnover in postmenopausal women with mild PHPT.[12–18] However, in elderly patients HRT is associated with problems of compliance or even safety.

Bisphosphonates are capable of suppressing parathyroid hormone (PTH)–mediated bone resorption in hyperparathyroidism and can be used as an adjunct for the acute medical control of severe hypercalcemia.[19–25] Moreover, bisphosphonates are useful for the prevention and treatment of postmenopausal osteoporosis and, recently, it has been shown that oral alendronate[26–29] and risedronate[30] have the capacity to reduce the incidence of osteoporotic fractures.

In this study we investigate the effects of oral treatment with alendronate on BMD and biochemical markers of calcium and bone metabolism in elderly women presenting osteoporosis and mild PHPT.

MATERIALS AND METHODS

Patients

Twenty-six elderly women aged 67–81 years presenting osteoporosis (defined as a lumbar and/or femoral neck BMD over 2.5 SD below the young normal reference range) and mild PHPT, as defined by the Consensus Development Conference on the management of PHPT,[11] were enrolled in three centers of northern Italy. All patients were unwilling or considered unfit for surgery because of advanced age or cardiovascular problems. Baseline characteristics and BMDs are shown in Table 1. Exclusion criteria were concurrent systemic illness, thyroid disease, hepatic or renal dysfunction (serum creatinine >1.9 mg/dl), and other disorders known to influence bone mass. The patients with active gastroduodenal ulcer or disturbances in the esophageal transit also were excluded as advised by the alendronate warning label. No patient had received estrogens, bisphosphonates, or other drugs interfering with bone or mineral metabolism for the last 18 months. The patients were randomized for treatment with either 10 mg of alendronate taken orally on alternate days (alendronate group) or no treatment (control group). In the original protocol, the chosen dose was 5 mg/day but this formulation was withdrawn from the Italian market and substituted with the 10-mg formulation exactly when we initiated the study. All patients were maintained on a controlled diet with a calcium intake of 800-1200 mg/day.

During the recruitment of the 26 patients for the treatment trial, 13 additional PHPT patients came under our observation. They were comparable to the patients recruited for the study for severity of disease but were somewhat younger (61 ± 4 years) and had the parathyroid tumor surgically removed (Table 1 and 2). In this group of patients the spine BMD was obtained before and 12 months after surgery.

The overall 39 patients were recruited within 12 months in the three centers equipped with either QDR1000 or -2000 (Hologic, Inc., Waltham, MA, USA). Each patient had the entire follow-up done in the same center. Informed consent was obtained from all the patients and the study was approved by a local ethics committee.

Clinical evaluation

Lateral spine radiography was obtained at study entry, and 3 patients (1 in the control group and 2 in the alendronate group) with severe osteoarthritis and scoliosis were excluded from subsequent spine density analysis. None of the patients had radiological evidence of thoracic or lumbar

TABLE 2. BASELINE BIOCHEMICAL VALUES (MEAN AND SD) IN THE TWO PROSPECTIVE GROUPS AND IN THE RETROSPECTIVE SURGICALLY TREATED PATIENTS

Parameters	*Reference range*	*Alendronate group*	*Control group*	*Surgical group*
s-Calcium[a] (mg/dl)	8.4–10.4	11.0 (0.4)	10.9 (0.3)	11.1 (0.5)
s-Phosphate (mg/dl)	2.6–4.6	2.9 (0.6)	2.6 (0.5)	2.6 (0.5)
s-PTH (pg/ml)	10–65	144 (52)	155 (28)	150 (66)
s-Bone-alkaline phosphatase (U/liter)	10–35	42 (12)	43 (9)	45 (9)
s-Osteocalcin (nmol/liter)	0.6–2.5	4.1 (1.3)	3.6 (1.6)	3.7 (1.2)
u-Calcium/creatinine (mmol/mmol)	0.06–0.54	0.59 (0.24)	0.60 (0.19)	0.64 (0.11)
u-D-Pyridinoline/creatinine (nmol/mmol)	3.0–8.0	9.8 (3.6)	11.2 (3.3)	10.1 (2.3)

[a] Serum calcium levels were adjusted for albumin levels.

vertebral fracture and/or variant femur anatomy that could affect the accuracy of bone density evaluation.

Fasting blood samples were obtained at entry and after 1, 3, 6, 12, and 24 months for measurement of serum calcium, phosphate, creatinine (standard multichannel autoanalyzers), and bone alkaline phosphatase (precipitation procedure with wheat-germ lectin; Boehringer Mannheim, Ingelheim, Germany). Serum calcium was corrected for albumin concentration. Urine samples also were obtained at the same time points for the determination of calcium and creatinine (standard multichannel autoanalyzers). Aliquots of serum and urine were kept at −80°C until analyzed for serum osteocalcin (radioimmunoassay [RIA] kit; Incstar Corp., Stillwater, MN, USA), intact PTH (Diagnostic Systems Laboratories, Nichols, CA, USA), and free deoxypyridinoline (Dpyr)/creatinine ratio (Metra Biosystems, Nichols, CA, USA).

BMD was measured using dual-energy X-ray absorptiometry (DXA; QDR1000 or -2000). Scans of whole body, lumbar spine (vertebrae L2–L4), and proximal femur subregions were obtained every 6 months and were analyzed using the manufacturer's software. In our laboratories, the precision of these measurements of BMD are 0.4% for the total body, 0.9–1.0% for the lumbar spine, 1.3–1.4% for the femoral neck, 2.7–2.9% for the Ward triangle, 1.6–1.7% for the trochanter, and 1.1–1.2% for the total hip.

Statistical methods

The significance of the percent changes in biochemical parameters and in BMD from baseline was evaluated by Student's *t*-test for paired observation. The comparison of the changes between treated and control patients was evaluated by analysis of variance (ANOVA) for repeated measures and then by Student's *t*-test for unpaired observation. Correlation was carried out using Spearman rank correlation (SPSS 8.0; SPSS, Inc., Chicago, IL, USA).

RESULTS

At study entry, the patients' clinical characteristics, BMDs, and biochemical values did not differ significantly between the two groups that had a medical follow-up (Tables 1 and 2). The patients who underwent successful parathyroidectomy were significantly younger (mean age, 61 ± 4 years; data not shown) than the patients in the other groups. All patients completed the first 6 months of follow-up. Three patients in the alendronate group dropped out during the first year either for gastric intolerance to the drug or for the discovery of breast cancer or for the necessity to introduce diuretic therapy. One patient of the control group was lost to follow-up during the second year for "in situ" endometrial cancer. In Table 3 the percent changes from baseline in biochemical parameters (mean ± SD) during the study are shown. Serum calcium, serum phosphate, and urinary calcium excretion remained fairly stable in the control group. In the alendronate-treated patients the biochemical variables significantly decreased during the first 3–6 months but rose back to the baseline values afterward. The decreases in serum calcium were associated with increases in serum PTH levels, which remained significantly increased over baseline during the first year of treatment. The mean percent changes from baseline in biochemical markers of bone turnover are shown in Fig. 1. Urine Dpyr excretion significantly fell within the first month of treatment in the alendronate group and remained suppressed at all times relative to baseline. The serum markers of bone formation alkaline phosphatase and osteocalcin fell more gradually and the decrease became significant after 3 months of treatment.

The BMD percent changes at all relevant skeletal sites in the two groups are shown in Fig. 2. A significant increase versus baseline was observed at all studied sites in the patients on alendronate. The changes already were statistically significant within the first 6 months of treatment in the "trabecular" sites (lumbar spine, trochanter, and Ward's triangle). A significant positive correlation was found between the changes in total body BMD at the first year and both baseline bone alkaline phosphatase and serum osteocalcin levels (correlation coefficients 0.84 and 0.64, respectively; $p < 0.05$, data not shown) in alendronate-treated patients. During the second year of treatment, a continuous trend to increase was observed at all skeletal sites. In the untreated patients BMD decreased at most skeletal sites but the changes were statistically significant only for total body and femoral neck after 2 years of observation. A significant

TABLE 3. BIOCHEMICAL CHANGES: PERCENT CHANGE FROM BASELINE (± SD) IN THE CONTROL AND ALENDRONATE GROUP

	1 Month		*3 Months*		*6 Months*		*12 Months*		*24 Months*	
Parameters	*Control*	*Alendronate*	*Control*	*Alendronate*	*Control*	*Alendronate*	*Control*	*Alendronate*	*Control*	*Alendronate*
s-Calcium	−0.5 (2.0)	−3.0 (5.5)	−1.1 (3.1)	−5.2 (4.0)*,†	−1.3 (4.4)	−3.2 (5.3)	−1.1 (4.5)	−1.9 (3.6)	+0.2 (3.1)	+0.6 (3.0)
s-Phosphate	+1.2 (10)	+0.4 (9.2)†,‡	−1.2 (11)	−6.0 (9.8)‡	−2.2 (15)	−2.8 (9.5)†,‡	+3.7 (24)	+0.5 (9.6)†,‡	+0.3 (24)	−1.3 (9.2)
s-PTH	−11 (11)	+24 (21)‡	−1.5 (23)	+36 (19)*,†	−9.0 (25)	+24 (25)‡	−13 (28)	+15 (20)†,‡	+5.4 (17)	+13 (29)
u-Calcium/creatinine	−0.1 (19)	−42 (16)*,†	+2.4 (25)	−39 (17)*,†	+2.5 (39)	−16 (26)	−6.8 (34)	−3.2 (19)	−0.3 (27)	+10 (25)

* $p < 0.001$ compared with baseline; † $p < 0.05$ between groups; ‡ $p < 0.05$.

FIG. 1. Percent changes in serum bone alkaline phosphatase, serum osteocalcin, and Dpyr urinary excretion in the control (dotted line) and alendronate-treated (continuous line) primary hyperparathyroid patients. The significance ($p < 0.05$) of the differences also is shown. ∘, versus baseline; ∗, between groups.

negative correlation was found between the changes in total body BMD and baseline serum bone alkaline phosphatase (correlation coefficient −0.69; $p < 0.05$). The correlation coefficients of the relationships between bone alkaline phosphatase and BMD changes in both treated and control patients did not change after adjusting for age or baseline BMD values. The differences between alendronate-treated patients and control patients were significant at all sites after 2 years of observation.

In the surgically treated patients, spine BMD increased by 6.7 ± 6.5% within a year (data not shown). This increase was superimposable (+7.0%) to that observed after 1 year of alendronate therapy. None of the patients complained of

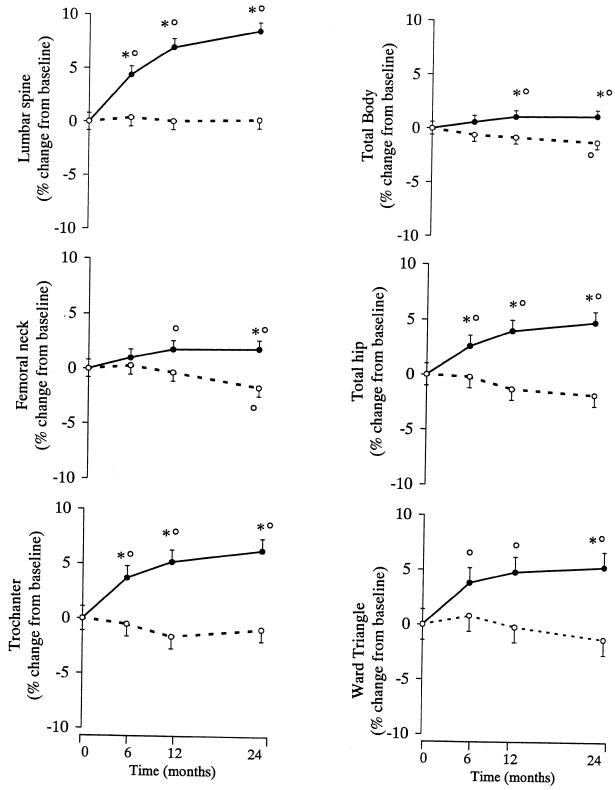

FIG. 2. Percent changes in BMD at the lumbar spine, total body, and hip sites in the control (dotted line) and alendronate-treated (continuous line) primary hyperparathyroid patients. The significance ($p < 0.05$) of the differences also is shown. ∘, versus baseline; ∗, between groups.

clinical vertebral or nonvertebral fracture during the period of observation.

DISCUSSION

We found that in patients with mild PHPT, the treatment with low oral doses of alendronate (10 mg on alternative days) was able to increase BMD at all the skeletal sites explored, independent of the structural prevalence of cortical or trabecular bone tissue. The 5-mg daily dose initially was chosen because this was the only dose recommended for the treatment of postmenopausal osteoporosis in Italy at the time when the study was submitted to the Ethical Committee and it is the daily dose recommended now for osteoporosis prevention in United States. The assumption that 10 mg alendronate on alternate days are equipotent to 5 mg/day made when the 5 mg of alendronate was withdrawn from the Italian market seems acceptable in light of the recent observation that 70 mg once weekly and 10 mg daily are therapeutically equivalent in the treatment of postmenopausal osteoporosis.[31] The observed increases in total body calcium indicate that the remarkable changes in the more trabecular sites did not come at the expense of cortical bone. The order of changes we observed with this relatively low dose of alendronate is comparable with that observed after estrogen-replacement therapy.[16–18] Bone density increases are somewhat more superior than those obtained with an equivalent dose (5 mg/day) of alendronate in osteoporotic patients,[26–28,32,33] and this might be related to the increased bone turnover of PHPT patients, which is known to be related to the densitometric increases during treatment with inhibitors of bone resorption.[34,35] In fact, the bone turnover markers were above the normal range in 45–62% of the patients. This hypothesis also is supported by the correlation we found between baseline serum osteocalcin and alkaline phosphatase and the BMD changes obtained after alendronate therapy. Recently, it also has been observed that the biochemical markers and the histomorphometric indices of bone turnover are significantly correlated with the bone densitometric gains achieved after successful surgical treatment of PHPT patients.[8] In our study the surgically treated patients were younger then those treated with alendronate, but even though they were not matched by design, the severity of bone involvement and baseline bone markers were similar and the order of BMD changes at trabecular sites in the alendronate-treated patients are similar to those consequent to the surgical correction of PHPT, as observed in this and in other studies.[4–9] The increases in femoral neck BMD after 2 years of alendronate therapy are lower than those (+6%) observed by Silverberg et al.[7] after parathyroidectomy but similar to those reported in other studies.[6,9]

The clinical relevance of the bone mass changes observed with alendronate therapy is uncertain and it is unknown whether changes of this magnitude would be of clinical importance for later fracture risk. Our study is far from being powered to detect changes in fracture rate and the risk of fracture in these patients with mild PHPT is still disputed.[1–3,36–40]

Alendronate therapy rapidly decreased the biochemical marker of bone resorption. The nadir was achieved by the sixth month and a 50% decrease has maintained all throughout the treatment period. The markers of bone formation decreased at a slower rate with a nadir around the twelfth month of alendronate therapy. The uncoupling between the markers of bone resorption and bone formation, particularly within the first 3 months, most likely was associated with intense positive bone balance, which explains the transient fall in serum calcium and urinary calcium excretion and the transient significant increase in serum PTH. The biochemical changes observed here are similar to those we obtained in an early study with oral clodronate in mild PHPT patients[23] and resemble those occurring after parathyroidectomy. It is then confirmed that at least in patients with mild PHPT the serum calcium-PTH feedback is preserved and that the decrease in serum calcium is transient and of little clinical relevance in these patients in whom hypercalcemia is not a major concern. The consequences of the transient PTH changes on bone metabolism remain uncertain, being potentially either positive or negative.

In the control patients of this study the biochemical markers of disease activity remained stable over the period of observation, but the BMD values slowly declined at the cortical sites (femoral neck and total body), and these de-

creases became significant at the end of the second year of observation. These results are similar to those observed in other longitudinal studies including postmenopausal women with PHPT[17,18] but in contrast with other published longitudinal data on BMD in untreated PHPT patients.[7,41–43] However, at variance with these latter studies, our patients were considerably older and the majority of them had some degree of physical disability associated with low physical activity.

In our study the correlation observed between baseline serum levels of bone alkaline phosphatase and the percent decline in total body BMD seems to indicate that the patients with the highest bone turnover were those loosing more bone. Similar correlation was reported by Guo et al.[18] using urinary cross-linked N-terminal telopeptide of type I collagen as bone turnover marker.

In conclusion, the results of this pilot study indicate that in postmenopausal women 10 mg of alendronate taken on alternate days significantly increases BMD at the most clinically relevant skeletal sites. The order of changes observed after 2 years of therapy are very close to those obtained within a few months after surgical correction of the disease. This result makes alendronate a good candidate as a supportive therapy in patients with mild PHPT who are unwilling or unsuitable for surgery, in whom osteoporosis is a reason of concern.

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