POSTMENOPOZAL OSTEOPOROZ TEDAVİSİNDE ALENDRONAT VE KALSİTONİNİN KEMİK YOĞUNLUĞU VE KEMİK DÖNGÜSÜ ÜZERİNE OLAN ETKİLERİNİN KARŞILAŞTIRILMASI

Serpil SAVAŞ[1]1, Abdullah CİNDAŞ[1], Berna OKUDAN[2], Mustafa ÖZTÜRK[3]

ÖZET

Bu çalışmanın amacı postmenopozal osteoporoz tedavisinde kullanılan 10 mg/gün oral alendronat ile 200IU/gün intranazal kalsitonin tedavilerinin kemik yoğunluğu ve kemik döngüsü üzerine olan etkilerinin karşılaştırılmasıdır. Postmenopozal osteoporozu olan 47 hasta 12 ay boyunca alendronat tedavisi, 30 hasta ise kalsitonin tedavisine alındı. Omurga ve kalça kemik mineral yoğunlukları (KMY) ve kemik döngüsü belirteçleri başlangıçta ve 12 ay sonunda ölçüldü. Tedavinin sonunda, alendronat tedavisi omurga (p=0,05) , büyük trokanter (p=0,04) ve femur boynunda (p=0,05) kalsitonin tedavisine göre daha fazla KMY artışına neden olurken, serum osteokalsin (p=0,0001) ve idrar deoksipridinolin (p=0,01) seviyelerinde daha fazla azalma oluşturdu. Bir yılın sonunda 10 mg/gün oral alendronatın postmenopozal osteoporozlu hastalarda 200 IU/gün nazal kalsitonine göre daha fazla lomber omurga ve kalça KMY artışı yaptığı ve kemik döngüsünü daha fazla baskıladığı sonucuna varıldı.

Anahtar sözcükler: Postmenopozal osteoporoz, alendronat, intranazal kalsitonin, kemik mineral yoğunluğu, kemik döngüsü

SUMMARY

COMPARISON OF THE EFFECTS OF ALENDRONATE AND CALCITONIN ON BONE DENSITY AND BONE TURNOVER IN THE TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

The aim of this study is to compare the effects of 10 mg daily oral alendronate and intranasal calcitonin at a daily dose of 200 IU on bone density and bone turnover in the treatment of postmenopausal osteoporosis. Forty-seven patients with postmenopausal osteoporosis received alendronate therapy and thirty patients received salmon calcitonin nasal spray for 12 months. Spine and hip bone mineral density (BMD) and markers of bone turnover were measured at baseline and at 12 months. Alendronate produced greater increases in BMD than calcitonin at 12 months at the spine (p=0,05) , greater trochanter (p= 0,04) , femoral neck (p=0,05) . Alendronate produced greater decreases in serum osteocalcin levels than calcitonin (p=0,0001) and urinary deoxypridinoline (p=0,01) . We conclude that in postmenopausal women with osteoporosis, 10 mg daily alendronate produced significantly greater increases in BMD of the lumbar spine and hip and greater decreases in bone turnover than intranasal calcitonin at daily dose of 200 IU at 12 months.

Key words: Postmenopausal osteoporosis, alendronate, intranasal calcitonin, bone mineral density, bone turnover

[1] Süleyman Demirel Üniversitesi Tıp Fakültesi Fiziksel Tıp ve Rehabilitasyon AD

[2] Süleyman Demirel Üniversitesi Tıp Fakültesi Nükleer Tıp AD

[3] Süleyman Demirel Üniversitesi Tıp Fakültesi Halk Sağlığı AD

INTRODUCTION

Postmenopausal osteoporosis is a common disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture risk (1). The clinical significance of osteoporosis lies in the fractures which arise, and for this reason it is acknowledged as a major problem of health care (2). Because a low bone mass is the major risk factor for fractures, the treatment of osteoporosis focuses on agents that prevent bone loss or even increase bone mass (3). Alendronate and calcitonin are the commonly prescribed antiresorptive drugs for the treatment of postmenopausal osteoporosis and both of these therapies have been reported to be associated with increases in BMD and decreases in bone turnover (4-10). A direct comparision is necessary to adequately understand the relative efficacy of these two therapies. Although the increases in BMD reported with alendronate, in general, greater than those reported with calcitonin, there is little data about the direct comparision of the efficacy of 10 mg daily alendronate and intranasal calcitonin at a dose of 200 IU (11). Thus, we planned this study to compare directly the effects of 10 md daily oral alendronate and intranasal calcitonin at a daily dose of 200 IU on bone density and bone turnover markers in patients with postmenopausal osteoporosis.

PATIENTS AND METHODS

Women were eligible to participate the study if they were postmenopausal for at least 1 year and lumbar spine bone mineral density was at least 2,5 SD below normal for normal women age 30 years at either the PA lumbar spine or femoral neck and no history of fractures. We excluded women with other causes of osteoporosis (e.g., treatment with glucocorticoids) or other disorders of bone and mineral metabolism (e.g., vitamin D deficiency, Paget's disease, or hyperparathyroidism), abnormal renal function (serum creatinine level, >1.5 mg per deciliter [130 µmol per liter]), or abnormal hepatic function or any prior treatment with bisphosphonates or treatment within the preceding 12 months with estrogen, progestin, calcitonin, fluoride, or an anabolic steroid.

Patients were randomly assigned to one of the following groups: oral alendronate sodium (Fosamax; Merck & Co.), 10 mg daily and intranasal calcitonin-salmon (Miacalcic Nasal Spray; Novartis), 200 IU daily. Forty-seven patients received 10 mg daily alendronate therapy and 30 patients received salmon calcitonin nasal sprey at a dose of 200 IU for the treatment of primary postmenopausal osteoporosis. Patients instructed to take alendronate tablet orally in the morning, at least 30 minutes before the first meal of the day with a glass of plain water, and to remain upright for at least 30 minutes after dosing and after the first food of the day. All participants received 1000 mg of calcium and 400 IU vitamin D to ensure a minimum daily intake of calcium and vitamin D.

Bone mineral density at the lumbar spine and hip (femoral neck and greater trochanter) was evaluated by dual x-ray absorptiometry using Norland-XR 2000 at baseline and 12 months.

All serum and urine specimens were collected in the morning after an overnight fast. Samples were stored at -70º prior to analysis. Biochemical markers of bone turnover were assessed at baseline and at 12 months. Serum osteocalcin was measured with immunometric assay (Immulite Osteocalcin, USA). Urinary deoxypyridinoline (adjusted for creatinine excretion) was mesasured by a solid phase chemiluminescent enzyme-labeled immunoassay (Immulite Pyrilinks-D,USA).

Table I. Baseline characteristics of the patients

	Alendronate group N=47	Calcitonin group N=30	p
Age (years)	59,1±9,6	58,8±8,9	0,8
Years since menopause (years)	16,3±10,1	15,2±9,0	0,3
Body mass index (kg/m^2)	27,4±4,1	28,8±4,5	0,1
Lomber spine bone mineral density (gr/cm^2)	0,77±0,1	0,81±0,10	0,07
Femoral neck bone mineral density (gr/cm^2)	0,68±0,11	0,69±0,10	0,6
Greater trochanter bone mineral density (gr/cm^2)	0,56±0,08	0,59±0,08	0,1
Serum osteocalcin (3,1-13,7 ng/ml)	17,94±10,06	18,95±12,35	0,7
F-Dpd:Creat (3,0-7,4 nmol/mmol)	8,7±3,7	9,5±3,3	0,4

STATISTICAL ANALYSIS

Analysis was performed using SPSS for Windows 11.0 software (SPSS, Chicago, IL). Baseline measurements were expressed as mean±standard deviation. Changes in BMD and bone turnover markers were expressed as mean percentage change. Within-group changes for BMD and bone turnover markers were evaluated by paired sample t test. Independent t test was used for the comparison of the groups for the changes in BMD and bone turnover markers. In all analyses, p values below 0,05 were considered significant.

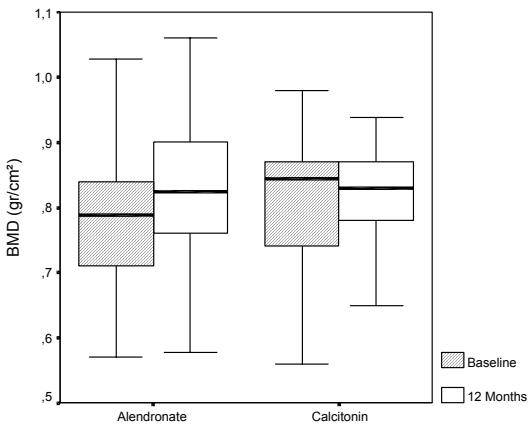
RESULTS

Baseline characteristics of the patients, including age, years since menopause, parity, body mass index, lumbar spine and hip bone mineral density, baseline biochemical markers of bone turnover were similar among the groups (Table I).

Thirteen patients (27,1%) in the alendronate group, 8 patients (26,7%) in the calcitonin group had a history of bilateral oophorectomy. Two patients (4,2%) in the alendronate group, 2 patients (%6,7) in the calcitonin group reported a family history of osteoporosis. Six patients (12,5%) in the alendronate group and 1 patient (3,3%) in the calcitonin group had current tobacco use. The percentage of patients with selected risk factors for osteoporosis was also similiar between the groups (p=0,9, p=0,6 and p=0,1 respectively).

BMD increased 6,9% at the lomber spine (0,82±0,10 gr/cm^2) , 3,8% at the femoral neck (0,71±0,08 gr/cm^2) and 7,3% at the greater trochanter (0,59±0,76 gr/cm^2) in the group treated with alendronate at 12 months. All of

A. Lomber spine BMD



B. Femoral neck

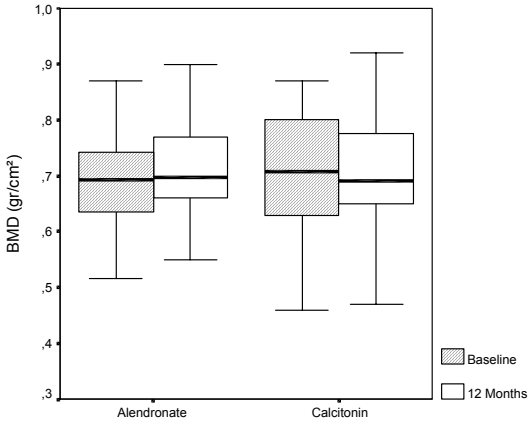
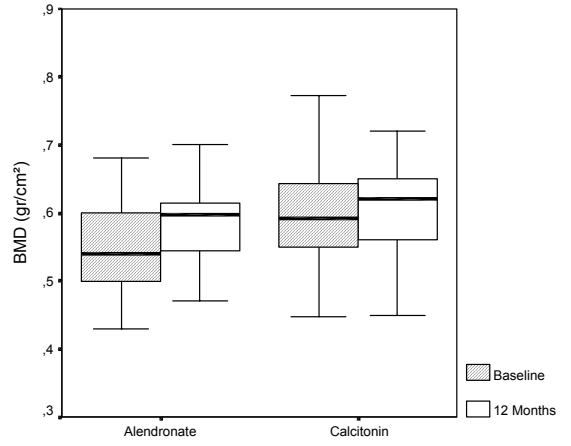


Figure 1. Boxplots showing BMD changes from baseline in A, the lumbar spine, B, greater trochanter. C, femoral neck, treated with alendronate and calcitonin

C. Greater trochanter



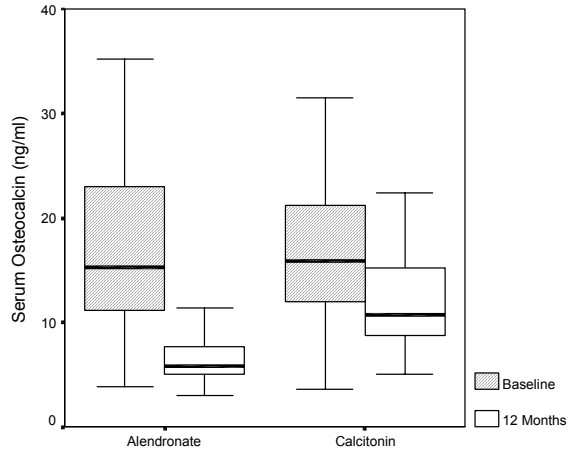


Figure 2. Boxplots showing serum osteocalcin changes from baseline

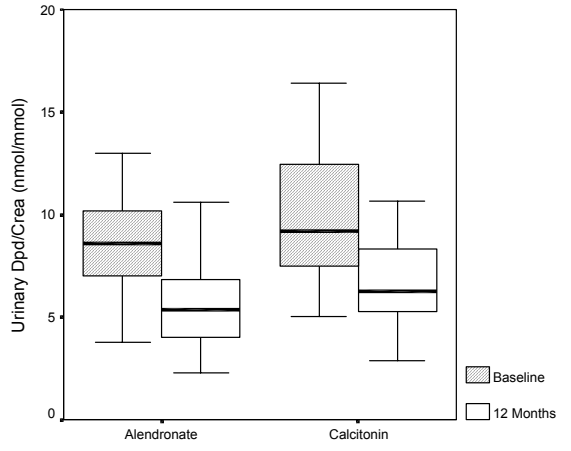


Figure 3. Boxplots showing urine deoxypridinoline/creatinine changes from baseline

the increases in BMD were statistically significant (p=0,001, p=0,004 and p=0,001, respectively. In patients treated with calcitonin BMD increased 1,8% at the lomber spine (0,83±0,10 gr/cm^2), increased 1,6% at the greater trochanter (0,60±0,07 gr/cm^2) and decreased 1,7% at the femoral neck (0,69±0,12 g/cm^2). None of these increases were not statistically significant (p=0,33, p=0,9 and p=0,6, respectively) . Alendronate increased the BMD of the lomber spine, greater trochanter and femoral neck better than calcitonin (p=0,05, p=0,05 and p=0,04, respectively) (Figure 1) .

Serum osteocalcin was reduced 56,7 % in the alendronate group (6,7±3,67 ng/ml, p=0,0001) and 19,73 % in the calcitonin group (12,2±5,07 ng/ml, p=0,007)). Urine deoxypridinoline/ creatinine decreased 33% in the alendronate group (5,6±1,97 nmol/mmol, p=0,0001)) and increased 4,69 % in the calcitonin group (9,8±9,02 nmol/mmol, p=0,95). Alendronate decreased serum osteocalcin and urine deoxy-pridinoline/creatinine better than calcitonin (p=0.0001, and p=0,006, respectively) (Figure 2,3) .

DISCUSSION

In this trial alendronate increased BMD at the spine and hip better than did intranasal calcitonin over 12 months. Our findings are consistent with the results of the only study which compares the treatment effects of alendronate 10 mg daily and intranasal calcito-nin 200 IU daily (11). In the previous studies with alendronate it was shown that alendronate increased BMD from baseline at 12 months 5-8 % at the lumbar spine, 2-5 % at the femoral neck and 4-7% at the trochanter (5, 9-12). Intranasal calcitonin at a dose of 200 IU daily was reported to increase BMD from baseline at 12 months by approximately 1-3% at the lumbar spine, 0% at the femoral neck and 2,5% at the greater trochanter in women at least 5 years of menopause (13,14) Your results are

also consistent with these previous data. In our trial BMD at the femoral neck was decreased 1,7% with intranasal calcitonin. A therapeutic benefit of calcitonin at the level of the cortical bone has been less well demonstrated than for the trabecular bone (4, 15) .

The decreases in biochemical markers were greater with alendronate than intranasal calcitonin in the present study as previously reported (11) . Alendronate at a dose of 10 mg has been reported to induce a 35-50% decrease in total deoxypyridinoline (16,17) and a 50% decrease in osteocalcin (16). Intranasal calcitonin modestly reduces bone turnover in women with osteoporosis (18). Intranasal calcitonin 200 IU decreases bone resorption in the magnitude of 15% after a single dose as well as after a multiple daily dosing regimen (19). Our results are consistent with these published data.

In this study, the comparision of the treatment effect of alendronate and intranasal calcitonin were based on bone mineral density, rather than fracture risk, as the primary end point. This was a limitation of this study. Although reduced bone mineral density is the strongest predictor of a fracture, there are several other risk factors for fractures. An increase in spine bone mineral density with antiresorptive drugs plays a role in reducing the risk of vertebral fracture, but other mechanisms, not measured by standart densitometry, are also important. Treatment with alendronate or intranasal calcitonin reduces the risk of vertebral fracture more than would be predicted by the increase in bone mineral density. In the Fracture Intervention Trial, improvement in spine bone mineral density explained 16% of the reduction in the risk of vertebral fracture with alendronate (1) . Because of these reasons with our results, we can not assume that alendronate's antifracture effect is greater than intranasal calcitonin.

The second limitation of the present study was not to use a plasebo group. As the effects of alendronate and intranasal calcitonin on BMD and bone turnover are very well known, we did not want to let a group of osteoporotic patients stay drug free for 12 months long.

In conclusion, this randomized trial comparing intranasal calcitonin and alendronate in postmenopausal women with osteoporosis demonstrated that alendronate better increased BMD at the spine, greater trochanter and femoral neck, and also 10 mg daily alendronate was more effective in suppressing bone turnover than 200 IU daily intranasal calcitonin at 12 months. Further studies are needed for the comparision of the antifracture effects of alendronate and intranasal calcitonin.

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