Influence of Alfa Calcidol Therapy on Bone Mineral Dansitometry (BMD) in the Postmenopausal Period

POSTMENOPOZAL PERİODDA a-CALCIDOLUN KEMİK MİNERAL DANSİTOMETRESİ ÜZERİNE ETKİSİ

Melike DOĞANAY*, Orhan S. AKSAKAL**, Leyla MOLLAMAHMUTOĞLU***, Oya GÖKMEN[1]

* Uz.Dr.,Dr.Zekai Tabir Burak Kadın Hastanesi,
** Dr,,Dr.Zekai Tahir Burak Kadın Hastanesi, Başasist.,
*** Dr.Dr.Zekai Tahir Burak Kadın Hastanesi, Şef Muav.,
**** Doç.Dr.Dr.Zekai Tahir Burak Kadın Hastanesi, Başhekimi, ANKARA

Summary

Objective: *Aim of this prospective study was to assess the influence of alfacalcidol therapy on BMD of postmenopausal patients.*

Design: *96 postmenopausal women (mean 50.2±1.3 years) within one year after menopause, were enrolled in the investigation. Indication of alfacalcidol therapy was to prevent the development of postmenopausal osteoporosis in such cases when oestrogen administration was contraindlcated or the patients refused the HRT.*

Material Methods: *Daily dose of alfacalcidol treatment was 0.5 meg. During the therapy serum calcium creatinine and urine calcium-creatinine ratio were determined. BMD was measured in lumbal spine (L2-L4) and femur neck with DXA method (LunarR) before and after 12 months alfacalcidol administration.*

Results: *During the therapy mean Z-scores measured in lumbal spine and in femur neck changed from (-1.12±0.27) to (-0.7¡±0.29) p<0.05).*

Conclusion: *This result indicates that alfacalcidol treatment has a positive effect on BMD in the postmenopausal period and it can prevent the development of postmenopausal osteoporosis if hormone replacement therapy is contraindicated.*

Key Words: Menopause, B M D

T Klin Jinekol Obst 1999, 9:135-140

Özet

Amaç: *Bu prospektif çalışmanın amacı, postınenopozal dönemdeki hastalarda a-calcidolun kemik mineral dcınsitometresi üzerine etkisini belirlemektir.*

Çalışmanın Yapıldığı Yer: *Dr.Zekai Tahir Burak Kadın Hastanesi, Menopoz Bölümü.*

Materyel veMetod: *96postınenopozal kadın (ortalama yaşları 50.2±1.3 yıl) menopoz başlangıcından 1 yıl sonra çalışmaya alındılar, a-calcidol tedavisinin endikasyonu postınenopozal osteoporozun önlenmesinde östrojen kullanımının kontrendike olduğu veya hastanın hormon replasmanını kabul etmemesi hali olarak belirlenmiştir. Günlük a-calcidol dozu (Alpha D³. TEVA) 0.5 mg olarak belirlenmiştir. Çalışma boyunca serum kalsiyum kreatiuin ve idrar kalsiyum/kreatinin oranları belirlenmiştir. Lumbal vertebra (L,-Lf ve femur boynu kemik mineral dansiteleri DXA metodu ile. (Lunar) 12 aylık periyodun başında ve sonunda ölçülmüştür.*

Sonuçlar: *Tedavi süresince ortalama lumbal (L^-L^ ve femur başını içeren Z-skoru ölçümleri (-1.] 2±0.27) ile (-0.7¡±0.29) (p<0.05) arasında değişim göstermiştir.*

Tartışma: *Bu sonuçlar a-calcidolun postınenopozal dönemde kemik mineral dansitesi üzerinde pozitif etkisi olduğunu göstermekte ve ayrıca hormon replasmaıt tedavisinin kontrendike olduğu durumlarda postmenopozal osteoporozu engeller görülmektedir.*

Anahtar Kelimeler: Menopoz, K M D

T Kim J Gynecol Obst 1999, 9:135-140

Osteoporosis is the most common disorder of bone estimated to affect 30 to 50% of postmenopausal women. Rapid loss of bone occurs in women at the time of menopause as a result of increased bone turnover and osteoclastic bone resorption that exceeds bone formation. Following this rapid phase, bone loss continues to progress, albeit at a slower rate. The associated microarchitectural deterioration includes the loss of connec-

Geliş Tarihi:

Yazışma Adresi: Dr.Melike DOĞANAY
Uzayan Sok. 5/2
Aydmlıkevler / ANKARA

tivity of trabecular bone which, together with loss of bone mass, results in a marked reduction in bone strength. Ultimately, there is an increased incidence of fractures, particularly with advancing age (1,2).

The continue and orosected morbidity and mortality associated with osteoporosis and the attendant social and economic implications of this disorder point to the need for additional safe and effective therapies (3).

We report the results of one year. Prospective, randomized, double-blind, placebo-controlled. The goals were to evaluate the safety, tolerability, and efficacy of daily, oral dosing of a-calcidol in osteoporotic postmenopausal women. Changes in bone mass of the lumbar spine and other skeletal sites were the principal out come measurements. The effects of a-calcidol therapy on biochemical indices of bone turnover and mineral homeostasis were also assessed (4).

Material and Methods

Subjects were women (mean 50.2±1.3 years) who were postmenopausal for at least one year and who had osteoporosis as defined by a low lumbar spine bone mineral density (BMD) (less than 0.92g/cm^2). These values are approximately 2.5 standard deviations below the mean BMD of mature premenopausal white women, they approximate the 30th to 40th percentile for BMD of 60 years old women. Pre-existing vertebral fracture was not a requirement for eligibility. These subjects were otherwise in good health based on their medical history. Physical examination, and laboratory screening evaluation and were no more than 15% below or 30% above ideal body weight. Their spinal anatomy was suitable for dual energy x-ray absorptiometry (DXA) of the lumbar spine, with at least three évaluable vertebrae from L_1 L_4. Subjects were informed of potential alternative treatments of osteoporosis and provided written informed consent. Criteria for exclusion included: 1) Metabolic disease known to alter skeletal or mineral metabolism, 2) Cancer, history of any illness, or significant end-organ disease that might confound the results of the study or pose additional risk to the subject, 3) History of on osteoporotic fracture of the proximal femur, 4) Active upper gastrointestinal disease, 5) Significantly impaired renal function (serum creatinine > 1.5 mg/dL), 6) Use of medications known to alter skeletal or mineral metabolism, 7) Daily use of medications which have appreciable potential for gastrointestinal irritation and 8) Use of any illicit drug, smoking of more than 20 cigarettes per day, habitual ingestion of greater than six cups of coffee per day, or more than two alcohol containing beverages per day.

This was a double-blind, randomized, placebo controlled study in which the primary objectives were to study the safety and tolerability of daily, oral dosing with a-calcidol for 1 year, and the effect of this compound on BMD of the lumbar spine, calcium-regulating hormones, and serum and urine biochemical indices of bone turnover. Secondary objectives were to determine the effect of a-calcidol on BMD at proximal femoral and other skeletal sites and on the incidence of vertebral fractures, progression of vertebral deformities and height loss.

Subjects were instructed to ingest either a- calcidol or plasebo tablets orally with 6 to 8 ounces of water each morning at least 1 hour before breakfast or other food or drink except water (or at least 3 hours after breakfast as a less desirable alternative) to ensure adequate absorption. They were intructed to remain upright for at least 1 hour after dosing. All subjects received a daily supplement of 500 mg elemental calcium.

Screening evaluations included a lumbar spine DXA, history, physical examination, hematology and chemistry profiles and screening mammography. Calcium intake was assessed by food frequency questionnaire at the start of study. Blood and urine samples were obtained at each visit to monitor safety and biochemical effects.

The primary efficacy endpoint was BMD of the lumbar spine measured by DXA. Secondary sites of BMD measurements included femoral neck, total hip, and total body. Due to differences in calibration among the machine types, results were expressed as percent change from baseline rather than as absolute changes.

The effect of a-calcidol on lumbar spine BMD was assessed for prespecified categorical variables (race, baseline-vertebral fractures, current smoking status, oophorectomy status, and creatinine clear-

ance) as well as for several continuous variables age, calcium intake, number of years postmenopausal, height, weight, body mass index, biochemical markers of bone turnover and lumbar spine BMD.

Serum and urine samples were obtained in the morning following an overnight fast every 3 to 6 months for assays of biochemical markers of bone turnover and mineral homeostasis. Serum alkaline phosphatase was measured as indices of bone formation activity. Serum and urine calcium, phosphate, creatinine, and alkaline phosphatase were assessed according to standart methods.

Results

Characteristics of the 96 postmenopausal women enrolled in the study are summarized in Table 1. Summary of baseline values for biochemical markers is presented in Table 2. There were no important differences between treatment groups at baseline with respect to these variables.

A summary of baseline values for BMD variables is presented by treatment group in Table 3. Summary statistics are presented by densitometer type with similarly calibrated types of densitometers grouped together. Some measurements could only be performed with some densitometer types: total hip., femoral neck., lumbar spine. There were no meaningful differences between treatment groups at baseline for BMD variables.

Efficacy variables in BMD from baseline are summarized in Table 3. Percent changes in BMD from baseline through one year are summarized in Table 4. After one year, a mean decrease from baseline in lumbar spine BMD of 0.8% was observed in subjects receiving placebo ($p<0.01$). In contrast, mean increases in lumbar spine BMD were observed in subjects receiving a-calcidol (5.4% in the 5 mg) (all $p<0.001$).

At the end of the first year, there was a mean decrease in lumbar spine BMD of 0.7% in the placebo group ($p<0.01$) and mean increases of 3.8 % in the 5 mg a-calcidol treatment group.

Femoral neck BMD decreased 1.6% in the placebo group after one year ($p<0.001$). Mean increases of 2.8% in the 5 mg a- calcidol treatment group. Total hip BMD decreased 0.9% over one

Table 1. Baseline characteristics in postmenopausal osteoporotic women treated with Alfa calcidol or placebo

	Placebo (n:94)	Treatment Group 0.50 meg (n:91)
Age (yrs)	59.3J-.3.6	53.6±4.1
Years since menopause	13.8±7.1	7.4±6.1
Height (cm)	152.6Ü0.4	154.3±3.0
Weight (kg)	64.6±5.9	66.8±8.5
BMI (kg/m.2)	28.Ü1.4	27.2±2.3
Estimated calcium intake (mg/day)	826±642	796±502

Data are the mean±SD

Table 2. Summary of baseline biochemical effiacay variables

	Treatment group	
	Placebo (n:96)	0.50 meg (n:91)
Serum alkaline phosphatase (U/L)	57±12	55±13
Serum calcium (mg/dl)	9.4±0.31	9.3±0.37
Serum phosphate (mg/dl)	3.8±0.3	3.7±0.4
Urine calcium/creatinine (mg/mg)	0.12±0.07	0.14±0.08

Data are the mean±SD

Table 3. Summary of baseline BMD efficacy variables

	BMD (g/cm2)	
Site	Placebo	0.50 meg
Lumbar spine	0.71±0.08	0.70±0.09
Femoral neck	0.59±0.09	0.58±0.08
Total hip	0.65±0.08	0.60±0.09

Date are the mean±SD for each treatment group

Table 4. Summary on mean change in BMD from baseline after one year

	BMD (g/cm²)	
Site	Placebo	0.50 meg
Lumbar spine	0.74±0.24[a]	5.53±0.42[a]
Femoral neck	1.50±0.40[a]	2.77±0.44[a]
Total hip	0.88±0.38<=	3.76±0.72[a]

Results are expressed as the mean percent change±SD
a: p<0.001 change from baseline
b: p<0.0l change from baseline
c: p>0.05 change from baseline

year in the placebo group ($p<0.05$). Mean increases of 5.1% in the 5 mg a-calcidol treatment group.

Discussion

This study demonstrates the effectiveness of oc-calcidol in restoring bone mass in postmenopausal women with statistically significant and clinically important gains at all key skeletal sites. These findings are consistent with previously reported positive effects of a-calcidol on bone mass and strength shown in several animal models and on bone mass in short-term and one year studies of osteoporotic postmenopausal women. In the present study, women receiving a-calcidol at each of one dose (5 mg) level experienced significant mean increases in lumbar spine B M D relative to both baseline and placebo-treated subjects. The increases in lumbar spine B M D in the a-calcidol treatment groups were most rapid during the first six months of treatment, with continued increases during the one year. Analysis of B M D of the spine showed increases in a-calcidol treatment group, confirming that there were true increases in bone mass and rejecting the possibility that subtle incident vertebral compression fractures could falsely inflate apparent B M D increases (5-7).

The initial gain in bone mass may be attributable to a decrease in bone turnover and concomitant filling of resorption lacunae with bone mineral (decreased bone remodeling space). This phenomenon has been referred to as a remodeling transient. Two potential explanations for the progressive increase in B M D with a- calcidol are either a continuing slow accretion of bone mineral in the remodeling space resulting from the reduction in bone turnover or a continued gain in bone mass by reversal of the postmenopausal resorption/formation imbalance at the basic multicellular unit (BMU) level. The former explanation is unlikely to account for progressive increases after about one year. It is more probable that a-calcidol progressively increases bone mass by allowing formation to exceed resorption, thus generating a net positive balance in skeletal mineral content (1,8-11).

The gains seen in lumbar spine B M D with a-calcidol therapy have the potential to substantially reduce the risk of vertebral fracture. Prospective epidemiologic studies of older postmenopausal women have shown that a one standart deviation (90%) difference in lumbar spinal B M D is associated with a 2.3-fold greater risk of vertebral fracture in those with lower B M D . Nonclinical studies of a-calcidol have consistently shown a positive correlation between bone mass and bone strength in treated animals. Therefore, one may hypothesize that the observed 13.2% positive effect of treatment with 5 mg of a-calcidol. Placebo after one year would ultimately result in a reduction in vertebral fracture risk of about 58%. Assuming that fracture risk decreases on the same time scale as B M D increases, the relative risk of incident vertebral fractures over the one year study would have been about 36%) lower in patients treated with a-calcidol than in those treated with, placebo. Although clinically important, the power to detect a 36% reduction in vertebral fracture risk in a study of this size was anticipated to be low. This 36% reduction in vertebral fracture was consistent with that anticipated by epidemiologic studies (9-14).

The rate of turnover in cortical bone is much lover than in trabeculer bone. This may explain the greater increase in B M D at the lumbar spine and femoral trochanter sites which have a higher propertion of trabecular bone than the femoral neck region, a- calcidol is the first agent to demonstrate a significant progressive annual increase in femoral bone mass (15-17).

The highly significant increase in femoral B M D would be expected to have a positive effect in reducing hip fractures. The increase in trochanteric B M D with a-calcidol was nearly as large as that seen at the lumbar spine. Assuming that increases in B M D produced by treatment with a-calcidol would be associated with a similar 2.8-fold lower fracture risk for each standart deviation in B M D observed in epidemiologic studies. We would expect that increases in femoral B M D of approximately as SD seen by the end of the one year of a-calcidol treatment would lead to 20 to 30% decrease in the risk of hip fractures (18).

Progressive loss of height due to vertebral fractures is characteristic feature of osteoporozis. Changes in stature have been used both to measure the natural history of osteoporozis and to serve as an efficacy end point in clinical trials. Although changes in stature are not always due to vertebral

deformity, this measure is on important manifestation of osteoporosis and attributable to vertebral changes in a blinded, placebo-controlled study once other reasons have been excluded. The loss of stature was significantly less over the 12 month course of the study for pooled data from all a-calcidol treatment groups vs. Placebo, indicating a positive effect of a- calcidol on a clinical end point that is a characteristic outcome of osteoporosis (19,20).

Decreases in bone turnover were observed in patients treated with a-calcidol as evidenced by the changes in the urinary calcium, serum alkaline phosphatase. The decrease in bone resorption in a-calcidol-treated subjects was sustained, dosedependent and non progressive. Inhibition of bone resorption by a-calcidol was reversible and appeared to be related to the current dose rather than the cumulative dose (6,15,16,19).

The magnitude of suppression of both bone resorption and formation is similar to that reported for estrogen-progestin therapy in postmenopausal women and results in a level of bone turnover similar to that of normal premenopausal women (8,12,15).

The decrease in bone resorption produced by a-calcidol, an anticipated, was associated a decrease in serum calcium which in turn resulted in a compensatory increase in PTH and 1,25-dihydroxyvitamin D, and decrease in serum phosphate and urine calcium. These changes gradually resolved during treatment. However, the small persistant decreases in serum calcium and phosphate after one year is consistent with the stable sustained reduction in bone resorption (3,9,11).

There were no consistent correlations between levels of biochemical markers of bone turnover and rates of BMD change in either placebo-or a-calcidol-treated subjects. This observation indicates that a- calcidol produced comparable increases in BMD in subjects regardless of the rate of bone turnover. This observation is in contrast to a report that the increases in BMD during treatment with salmon calcitonin are much larger in subjects with higher rates of bone turnover, and that subjects with low bone turnover do not respond well to calcitonin. Correlation between baseline BMD and other parameters should be viewed with caution as they are made for a patient population selected because spine BMD was abnormally low (8,10,14).

Subgroup analyses indicate a remarkably uniform spine BMD response to a-calcidol treatment in subjects with mild renal insufficiency or those who are more that 65 years old.

All doses of a-calcidol in this study were generally well tolerated. Although the overall incidence of clinical adverse experiences was high in both placebo and treatment groups, this finding is consistent with expectations for an older population in a carefully monitored clinical trial of one year duration. Moreover, no significant differences were seen between any a-calcidol group and the placebo group in the incidence of overall, serious or drug-related clinical adverse experiences. The frequency of discontinuation due to specific categories of adverse experiences was similar in the treatment and placebo groups.

Nonvertebral fractures occured at the anticipated low frequency and there were no significant trends in fractures among the treatment groups. No fractures were considered by the investigators to be drug-related, and there were no reports of stress fractures. The cumulative incidence of nonvertebral fracture results (in which the results of this study were pooled with results from a second study of identical design and similar size) were favorable with 8.5% and 10.7% in the a-calcidol and placebo groups respectively.

These results with a-calcidol compare favorably to those of other agents used for the prevention and treatment of postmenopausal osteoporozis althoughy there is very little comparable information avaible from one year, double-blind, placebo-control. Led trials. Increases in spine bone density of up to 5% in one year have been reported for ostrogen. Increases of 2 to 5% in 2 years have been reported for cyclic etidronate, and parenteral salmon calcitonin. Intranazal calcitonin produced a more modest increase in lumbar spine bone mineral density.

In summary, daily oral a-calcidol at all doses in this study produced statistically and clinically significant increases in BMD of the lumbar spine. Proximal femur and total body in postmenopausal osteoporotic women. The 0.5 mar. dose produced maximal BMD effectes, had an excellent safety

profile and was generally well tolerated. This is the first treatment which has produced a significant increase in femoral bone mass and progressive increases at most skeletal sites for one year in postmenopausal osteoporotic women. All a-calcidol doses reduced bone turnover and produced changes in biochemical indices of mineral metabolism which were in keeping with the effects of a specific inhibitor of bone resorption. The B M D increases over one year observed in the current study are predicted to result in clinically important reductions in the risk of vertebral (by about 40%) and nonvertebral (20 to 30%) fracture. Thus, a-calcidol appears to be a promising new the therapy for the treatment of osteoporosis in postmenopausal women.

REFERENCES

1. Consensus development conference: Diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med 1993; 94: 646-50.
2. Parfitt Am. Pathophysiology of bone fragility. Proc Fourth international symposium on osteoporosis. Hong Kong 1993; 543: 164-6.
3. Osteoporosis. Who should be treated? Proceedings of a symposium. Am J Med 1995; 98 (ZA).
4. Fleisch H. Mechanism of bone loss and mode of action of antiabsorbtive therapy. Osteoporosis international 6: (Suppl. 1) 1996 abs. No: 0 Su 001 s:84.
5. Delmas PD. Biochemical markers of bone remodelling osteoporosis international 6: (Suppl. 1) 1996 abs. No: omo 026 s:90.
6. Kanis J.A. Osteoporosis. Blackwell Science 1994; 185-227.
7. Riggs BL. Hodgson SF. Fallon WM et al. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. N.Eng J Med 1990; 322-802.
8. Riggs BL. Melton LJ. The prevention and treatment of osteoporozis. The N.Eng J Med 1992; 327: 61.
9. Reid IR, Ames RW, Evans MC et al. Effect of calcium supplementation on bone loss in postmenopausal women. The N. Eng J Med 1993; 328-460.
10. Lidor C, Sagiv P. Amdur B. Et all. Decrease in bone levels of 1.25 dihydroxy-vitamin D in women with subcapital fracture of the femur. Calcif Tissue Int 1993; 52: 146.
11. Haussier M R. Donaldson C A, Allegretto E A, et al. New action of 1.25 dihydroxy-vitamin D3 possible clues to the pathogenesis of postmenopausal osteoporosis. Copenhagen international symposiuman osteoporosis. Copenhagen Denmark 1984; 74.
12. Heaney RP. Bone mass. Nutrition and other lifestyle factors. Am J Med. 1993; 95: suppl SA:295.
13. Chapuv MC, Arloft ME. Duboeuf F et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. N Eng J Med 1992; 327: 1637.
14. Cormir C. Epidemiology, diagnosis and treatment of osteoporosis. Current opinion in Rheumatology 1994; 6: 329-35.
15. Tilyard MW, speras GFS, Com B et al. Treatment of postmenopausal osteoporozis with calcitriol or calcium. N Eng J Med 1993; 328: 460-4.
16. Mona S Calvo, David R Evre, Caren M. Gundberg: Molecular basis and clinical application os biological markers of bone tum over. Endoc Reviews 1996: 17:4, p:333-**68.**
17. Hagivara Satoshi, Yong Seoung-oh. Güter Claus C. Ben david Eli, Genant Harry K. Noninvasive bone mineral density measurment in the evalution of osteoporozis. Rheuat Disease Clin North Amer 1994: 20:3: 651-69.
18. Eastell R: Assesment of bone density and bone loss. Osteoporozis Int suppl 1996; 2: 53-4.
19. Alexandre C. Diagnosis and treatment of osteoporozis: Curr. opin Rheumatol 1995; 7 (3): 240-2.
20. Gombert SR, Schultz B M, Handy R C. Osteoporosis clinical features. Prevention and treatment. Endoc Metab North Amer 1995; 24 (2): 317-71.