

EXTENDED REPORTS

Effects of cyclical etidronate combined with calcitriol versus cyclical etidronate alone on spine and femoral neck bone mineral density in postmenopausal osteoporotic women

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Abstract

Objectives—Few data are available on the effects of combination therapy for the treatment of osteoporosis. The aim of this study was to compare the effects of intermittent cyclical etidronate (E) therapy alone with a combination of cyclical etidronate and calcitriol (E+C) on spine and femoral neck bone mineral density (BMD) at one year.

Methods—Postmenopausal women with at least one non-traumatic vertebral fracture or z score < -1.5 were randomly allocated to an E group (each cycle = oral etidronate 400 mg daily for 14 days followed by calcium 500 mg daily for 76 days) or an E+C group (as for E plus oral calcitriol 0.5 µg daily). Lumbar spine and femoral neck BMDs were measured by dual energy x ray absorptiometry at baseline and at one year. The study design did not contain a placebo group.

Results—The mean % increase in lumbar spine BMD was 5.2% (95%CI= 3.4 to 7.0) in the E+C group (n=24), which was significantly greater than the 2.7% (95%CI= 1.3 to 4.1) increase in the E group (n=23) (p<0.05). The femoral neck BMD in the E+C group increased by 2.0% (95%CI= 0.8 to 3.2), which was significantly different from the E group where there was a -0.4% (95%CI=-2.4 to 1.6) change (p=0.046).

Conclusions—These data show that a combination of cyclical etidronate and calcitriol is better than cyclical etidronate alone in terms of changes in BMD at both spine and femoral neck sites. Although further data are needed on fracture efficacy, this study suggests that combination therapies have additive therapeutic potential that may exceed that expected from their theoretical mode of action.

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mineral density (BMD) and may decrease vertebral fracture rates¹⁻³ although its effects at the hip are less clear. There is also some evidence that calcitriol (1,25-dihydroxyvitamin D₃), a vitamin D analogue, may reduce vertebral fracture rates,⁴ and a combination of vitamin D₃ and calcium supplements can reduce the risk of hip fractures and increase hip BMD in elderly women.⁵ Few data are available on whether a combination of bisphosphonate and vitamin D or its analogues is better at preventing bone loss or reducing fracture risk than either treatment alone. The aim of this study was to compare the effects of intermittent cyclical etidronate (E) therapy alone with a combination of intermittent cyclical etidronate and calcitriol (E+C) on lumbar spine and femoral neck BMD at one year in postmenopausal women with osteopenia and/or non-traumatic vertebral fractures.

Methods

The subjects were white postmenopausal women referred to the osteoporosis clinic. Lateral thoracic and lumbar spine radiographs (two films) were performed in a standardised manner, at a target to film distance of 101 cm centred at T9 and L3 respectively. Lumbar spine (L1-L4) bone mineral density (LSBMD) and femoral neck bone mineral density (FNBMD) were measured using dual energy x ray absorptiometry (DXA) (Hologic QDR/1000W). The precision of the latter in our department, based on repeated measurements on 20 women volunteers, is 0.6% for the lumbar spine and 1.3% for femoral neck. The following investigations were performed to exclude secondary causes of osteoporosis: full blood count, erythrocyte sedimentation rate, urea and electrolytes, liver function tests, calcium, phosphate, alkaline phosphatase, thyroid function tests, serum electrophoresis and Bence-Jones protein.

Inclusion criteria for the study were those women with either a minimum of one non-traumatic vertebral fracture (defined as a 25% reduction in vertebral height calculated from the anterior, posterior or central heights of adjacent vertebrae) or those with a BMD that

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Previous studies have suggested that treatment with etidronate, a bisphosphonate, in an intermittent cyclical form can increase spine bone

Table 1 Baseline data of the intermittent cyclical etidronate alone group (E) and the combined intermittent cyclical etidronate and calcitriol group (E+C)

Baseline data (SD)	E	E+C	p Value
Age (y)	66.6 (8.0)	66.0 (8.7)	0.8
Weight (kg)	60.6 (8.4)	56.9 (6.5)	0.1
Height (cm)	157.3 (6.2)	156.9 (4.8)	0.8
LSBMD (g/cm ²)	0.686 (0.138)	0.688 (0.121)	0.9
FNBM (g/cm ²)	0.571 (0.059)	0.551 (0.073)	0.3
Mean number of vertebral fractures	1.9 (1.6)	1.8 (1.8)	0.8
Years from menopause	19.8 (6.4)	18.7 (9.2)	0.7

was one and a half standard deviation below the mean for their age based on the DXA manufacturers database (z score < -1.5). The latter criteria were chosen arbitrarily, based on local treatment guidelines, as the study was started shortly before the World Health Organisation (WHO) definitions of osteoporosis were published. Nevertheless all patients recruited had a t score < -2.5 (BMD more than 2.5 standard deviation below the mean peak bone mass; which is confirmed osteoporosis on WHO criteria) at either the lumbar spine or femoral neck. Exclusion criteria were those women with malignancy, myeloma, thyroid dysfunction, biochemical evidence of hypo- or hyperparathyroidism, renal or liver impairment, evidence of malabsorption, history of gastrectomy, and those taking any drugs affecting calcium and bone metabolism including corticosteroids, thyroxine, diuretics, calcium and vitamin D supplements, hormone replacement therapy, bisphosphonates, and anticonvulsants.

Those women satisfying the entry criteria for the study were randomly allocated (sequential random numbers method) to an E group (repeated cycles consisting of oral etidronate 400 mg daily for 14 days followed by calcium carbonate 1.25g (equivalent to 500 mg of calcium when dispersed in water) daily for 76 days) or to an E+C group (as for E plus oral calcitriol 0.5 µg single daily dose throughout the cycle). The E+C group had the same amount of calcium supplementation as the E group. The treatments were continued for 12 months after which DXA using the same machine as at baseline were performed. Serum biochemistry including calcium concentrations were checked at three monthly intervals. Treatment arms were not blinded and placebo not used but the DXA scan technicians were unaware of the allocations.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS). Analysis of variance was used to determine whether there were any significant differences between the two treatment groups in terms of baseline characteristics including age, weight, height, time from menopause, number of vertebral fracture, lumbar spine and femoral neck BMDs. The primary end point was percentage change in BMD after one year.

Results

Fifty eight women (28 in the E group and 30 in the E+C group) were randomised in the study (age range= 42–85 years) of which 47 completed the 12 months of treatment (23 in the E group and 24 in the E+C group). Of the five

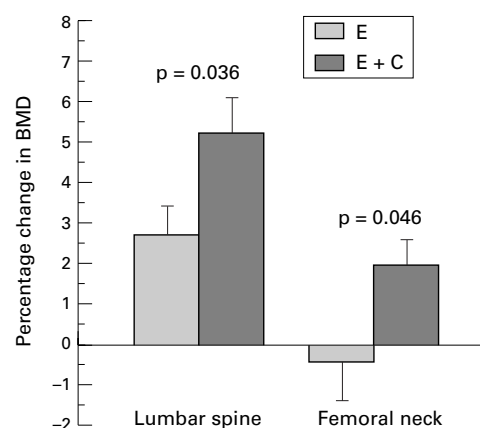


Figure 1 Percentage change in lumbar spine and femoral neck BMD at one year for the intermittent cyclical etidronate (E) and combined intermittent cyclical etidronate and calcitriol (E+C) therapies.

women withdrawn from the E group three developed minor gastrointestinal side effects, one could not tolerate the calcium supplements and one was given a thiazide for hypertension by her primary care physician. Of the six women withdrawn from the E+C group, one developed an acute vertebral fracture after only one week of being randomised and required calcitonin injections for pain, one developed a mild rash thought to be related to the etidronate, one developed minor gastrointestinal side effects, one was changed to hormone replacement therapy at one week at the request of the patient, one moved abroad and was therefore lost to follow up, and one developed mild asymptomatic hypercalcaemia (corrected serum calcium = 2.72 mmol/l; upper normal range in our hospital= 2.60 mmol/l), which resolved soon after the treatment was stopped. Serum creatinine concentrations remained in the normal range for all subjects.

Table 1 shows the baseline characteristics of the two treatment groups (study completers). There were no significant differences in these parameters between the two groups.

Figure 1 shows the mean (SEM) percentage changes in BMDs at one year for both treatment groups. Both groups had a significant increase in lumbar spine BMD at one year. At the lumbar spine site there was a 5.2% (95%CI= 3.5 to 6.9) increase in BMD for the combined E+C treatment group, which was significantly greater than the 2.7% (95%CI= 1.3 to 4.1) increase for the E (etidronate alone) group (p=0.036). At the femoral neck site there was a 2.0% (95%CI= 0.8 to 3.2) increase in BMD for the E+C group compared with a 0.4% (95%CI= -2.4 to 1.6) decrease for the E group, the differences between the two treatment groups being statistically significant (p=0.046). The differences in mean percentage change between the two groups for the lumbar spine and femoral neck sites were 2.5% (95%CI=0.2 to 4.8) and 2.4% (95%CI=0.1 to 4.7) respectively. Intention to treat analysis was not possible as those women withdrawn from the study did not have a follow up DXA at one year. After adjusting for age, weight, height, time from menopause, number of fractures,

and baseline BMDs using analysis of covariance, the differences in mean percentage changes in BMD at both lumbar spine and femoral neck sites remained significant ($p < 0.05$).

Discussion

Bisphosphonates, inhibitors of bone resorption, are increasingly being used for the treatment of osteoporosis. Studies have suggested that intermittent cyclical etidronate can significantly improve spinal bone mass^{1-3 6-9} and may lead to a decrease in vertebral fracture rates in postmenopausal women.¹⁻³ As yet there is no clear evidence that cyclical etidronate can reduce hip fracture rates, although prospective studies with the required large numbers and power to answer this question have not been performed. Some studies, however, have shown that hip bone mass can be increased with cyclical etidronate although generally to a lesser degree than at the spine.^{3 8 9}

There is also increasing evidence on the role of vitamin D and vitamin D analogues in treating osteoporosis. A French trial found that after daily combined treatment with 800 IU of vitamin D₃ and 1200 mg calcium for 18 months, hip fractures were 43% lower and non-vertebral fractures were 32% lower in elderly housebound women when compared with placebo.⁵ Bone mineral density of the total proximal femoral region increased by 2.7% in the treated group and decreased 4.6% in the placebo group ($p < 0.001$). Ooms *et al* have shown that by giving elderly Dutch women 400 IU of vitamin D₃ daily, without calcium supplementation, the femoral neck bone density increased modestly by over 2% after two years¹⁰ although no significant effect on hip fracture rates was seen.¹¹ In the observational MEDOS study, no overall effect of vitamin D treatment on the risk of hip fracture was shown. However, analysis of a subgroup of older patients with low body mass index demonstrated a significant reduction in fracture risk.¹² These studies have looked at "physiological" doses of vitamin D. The concept of treating osteoporosis with activated forms of vitamin D (vitamin D analogues) should be considered separate from the physiological vitamin D.

Studies investigating the effects of vitamin D analogues on bone mineral density have been conflicting indicating the inconsistency of responses when used as a monotherapy. With calcitriol, at doses of 0.8 and 0.62 µg daily respectively, lumbar spine BMD increased by 0.18%¹³ and 1.94%¹⁴ at two years, compared with bone loss of approximately 4% in placebo. In contrast Ott and Chesnut found calcitriol at a lower mean dose of 0.43 µg daily to have no significant effects.¹⁵ Further analysis, however, suggested a dose related effect at high dose (> 0.6 µg daily).¹⁶ Smaller studies using another vitamin D analogue alfacalcidol have shown a beneficial effect in preventing bone loss from the lumbar spine and decreasing the risk of vertebral fractures, although these studies were in Japanese subjects and it is not clear whether

the findings can be generalised to other populations.^{17 18}

There are few data on combined bisphosphonates and vitamin D analogues. A combined cyclical regimen, consisting of a five day activation period with calcitriol, followed by 20 days of etidronate 400 mg followed by 65 days without treatment, in postmenopausal women ($n = 100$) showed a significant increase in spine BMD and reduction in vertebral fracture rates over four years compared with the control group where a decrease in BMD was observed.¹⁹

Our data show that a combination of intermittent cyclical etidronate therapy and calcitriol was significantly better than intermittent cyclical etidronate therapy alone in terms of changes in bone density after one year at both the hip and spine sites. In the cyclical etidronate alone group lumbar spine BMD increased by 2.7% at one year whereas there was no significant change in the femoral neck BMD. In the combined treatment group the lumbar spine BMD increased by 5.2% and the femoral neck BMD also increased by 2.0%. It is unlikely that the 11 withdrawals biased our results as the numbers withdrawn were similar in both groups. The combined treatment was well tolerated and only one woman out of those randomised to the E+C group (3.3%) developed a mild asymptomatic hypercalcaemia, which resolved when the treatment was discontinued.

This study has several limitations. Firstly, it was a pragmatic trial mimicking an osteoporosis clinic situation without blinding or a placebo arm. However, given the objective outcome of BMD and the similarity of the groups after randomisation it is not clear that any bias would have acted in a specific direction. We did not have a placebo arm as we felt it difficult ethically to justify denying these osteoporotic women some recognised treatment for osteoporosis. Secondly, the study was not designed to detect differences in fracture rates, which would have required a study with much greater power, but was designed to detect changes in BMD between the two groups using similar magnitude of numbers used in previous studies showing changes in BMD with calcitriol. Thirdly, urinary calcium excretion was not measured in this small study, but because hypercalciuria is a recognised complication of calcitriol any future studies on combined treatment should investigate this issue. Fourthly, the study was not designed to elucidate the mechanism of action of the combined therapy. As we did not measure 25-(OH)-vitamin D or parathyroid hormone levels we cannot determine if subclinical osteomalacia or secondary hyperparathyroidism may have been present in some of our subjects, although if the latter was important the process of randomisation should have eliminated bias between the two groups. The precise mechanism of action of the combined therapy is therefore unclear. As calcitriol can stimulate both bone resorption and intestinal calcium absorption, in a given patient either of these actions could dominate leading either to a gain or loss of bone mass, which may

explain the inconsistency of studies using this drug as a monotherapy. It may be that calcitriol has a beneficial effect in the context of co-administration with a bisphosphonate, because any stimulation of bone resorption is blocked by the presence of the bisphosphonate.

As the study only lasted 12 months, it is probable that we were largely measuring remodelling transients. It may be that the combined therapy had more effect on the remodelling space by some mechanism related to their mode of action and interactions between each agent. In addition to its effects on calcium absorption²⁰ and on bone resorption,²¹ calcitriol may have a weak effect on bone formation through stimulation of osteoblastic activity.²² Further understanding of the effects of the various vitamin D receptor genotypes^{23, 24} may also be important in elucidating calcitriol's actions.

Nevertheless the results of this study point to the potential of combined therapies for osteoporosis and suggest different modes of action of the two drugs. As with all combined regimens larger longer term studies are needed to fully assess safety, mechanisms, and fracture rates.

In conclusion, combined treatment with cyclical etidronate and calcitriol was better than cyclical etidronate alone in terms of BMD changes at both spine and hip in postmenopausal women with osteoporosis.

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