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Effect of Etidronate on Urinary Calcium/Creatinin Ratio in Postmenopausal Women: A Prospective, Randomized, Placebo Controlled Study

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Abstract: There are both histomorphometric and nonhistomorphometric studies confirming that etidronate reduces bone resorption. In this study, we have examined urinary Calcium/Creatinine ratio (uCA/Cr) as a biochemical marker of bone turnover to show the effectiveness of etidronate and whether it could be used as a follow–up parameter of treatment. Eighty–one postmenopausal women aged 40 to 65 included into the study to investigate the effects of etidronate on uCa/Cr in a prospective, randomised, placebo controlled clinical trial. All necessary criteria matched 81 women were divided into 3 groups at random, each group consisted of 27 patients. Prior to treatment, uCa/Cr was calculated from all subjects 3 hours after drinking 1 liter of water in the morning. Twenty seven (33.3%) women were randomised to oral doses of etidronate (400 mg/day for two weeks followed by drug free period of 10 weeks), twenty seven women to etidronate (400 mg/day for two weeks) plus calcium (1000 mg/day) for the following 10 weeks and twenty seven women to placebo (Fe, 50 mg/day) for 12 weeks. After 12 weeks of treatment, uCa/Cr declined significantly in the etidronate group from 0.118±0.064 to 0.053±0.021, in etidronate+calcium group from 0.08±0.03 to 0.06±0.015 ((p=0.004) and (p=0.005), respectively). In the placebo group no significant change was observed (p=0.03). In conclusion, etidronate is effective in postmenopausal women and the effectiveness of treatment may be followed up by measuring uCa/Cr which is a simple and cheap parameter of determining the effectivensess of etidronate in prevention of osteoporosis. However, since there are contradictory findings concerning uCa/Cr exist, larger clinical and prospective studies should be carried out.

Key Words: Etidronate, urinary Calcium/Creatinin ratio, Hormone replacement therapy.

Introduction

The loss of ovarian hormones in menopause is a major risk factor for osteoporosis (1–2). It has been estimated that the risk of a woman developing fractures later in life is as great as that of cardiovascular disease and six times higher than that for breast cancer (3). Prevention of bone loss with hormone replacement therapy (HRT) has been shown to reduce the incedence of vertebral and hip fractures (4–5). However, HRT is associated with risks, some of which are well documented, whereas others (such as an apparent increased incidence of breast cancer) remain unproven. Side effects, such as withdrawal bleeding, together with concerns for long–term safety, limit the acceptability of long–term estrogen treatment (6). It has, therefore, been of great interest to find new therapies that can prevent the postmenopausal bone loss in younger and elderly women and eventually decrease the incedence of fractures. Since 1970's, biphosphonates have been in use for prevention of osteoporosis, especially in the treatment of tumor–induced hypercalcemia (7) and for the treatment of bone metastases as the essential pathogenic role of osteoclasts in tumor–induced osteolysis is now well established (8). Biphosphonates, analogues of inorganic pyrophosphate, a naturally inhibitor of bone mineralization, strongly bind to the bone mineral, hydroxyapatite, thus inhibiting resorption (9) and potentially affecting mineralization as well (10). A variety of treatment regimens employed continuous (11) or intermittent (12, 13) oral biphosphonate administration. These antiresoptive agents include drugs such as etidronate, pamidronate,

alendronate, coldronate, which have been shown to inhibit osteoclastogenesis and to cause apoptosis of active osteoclasts (14). The first biphosphonate to be investigated in large clinical studies was etidronate and its eficacy and safety of cyclical etidronate in the treatment of established osteoporosis is well established (12). Since continuous oral treatment with high doses of etidronate may lead to impairment of bone mineralization and the cessation of bone remodeling, a more ideal therapeutic regimen might consist of the intermittent cyclic administration of etidronate at a dose that inhibits bone resorption yet does not prevent mineralization (12). Biochemical parameters of bone resorption can be used for a sensitive and specific assessment of the osteolysis and also the effect of the drug administered to treat osteoparasis (15). The markers of bone resorption are pyridinoline, CroosLaps, hydroxyproline and urinary calcium (uCa), whereas, alkaline phosphatase (ALP) and osteocalcin are the markers of bone formation. Among those nonhistomorphometric parameters, urinary excretion of calcium is the classical and widely available parameter (15). In this sudy, we have investigated the efficacy of etidronate on osteoporosis by measuring uCa/Cr which is a simple and cheap parameter. In addition, we searched its usefulness for assessment of effectiveness of etidronate on osteoporosis.

Material and Method

Eighty–one women with natural or surgical menopause aged 40 to 65 were studied. Patients who had hysterectomy and bilateral oophorectomy included provided that FSH was in the postmenopausal range. Exclusion criteria were: any disease known to affect bone metabolism; treatment with calcitonin, vitamin D (at doses > 400 U/day), elemental calcium (at doses > 500 mg/day), carticosceroids, or anabolic steroids within the past 6 months; treatment with estrogens and/or progestagens within the past year. Patients were weighing between 49 and 87kg and within 20% of their normal body mass index (BMI<29 kg/m^2).

Blood and urine samples were obtained after 12 h fast from all patients. Serum chemistry included calcium (Ca), creatinin (Cr) and ALP and urinary Ca and Cr were assayed by Olympus AU 600 autoanalyser. Serum FSH, LH, estradiol were measured by chemiluminescence (Immulite; DPC). Urine samples were collected 3 hours later, after drinking 1 liter of water in the morning, to assay uCa/Cr (16). Following the biochemical work–up, all subjects were treated as they were randomly allocated to. Twenty seven (33.3%) women were randomised to oral doses of etidronate (400 mg/day for two weeks followed by drug free period of 10 weeks), twenty seven women to editronate (400 mg/day for two weeks) plus calcium (1000 mg/day) for the following 10 weeks and twenty seven women to placebo (Fe, 50 mg/day) for 12 weeks and followed up prospectively.

At the end of three months of treatment, using the same tecniques, serum Ca, ALP, Cr levels and uCA/Cr were measured. FSH, LH, E2 levels and pretreatment and posttreatment demographic values of serum Ca, ALP, Cr and uCa/Cr were analysed. Paired–t test, one way analyses of variance (ANOVA) and Neuman–Keuls comparison tests were used for statistical analyses. $p<0.05$ value was accepted as statistically significant.

Results

Results were given as mean values ±SD. The mean demographic data are shown in Table 1 and all groups were comparable with respect to all demographic data (p=0.496, p=299, p=0.32 and p=0.34 respectively) (Table 1). Also no significant difference between three groups in terms of E2, FSH and LH levels was seen (p=0.689, p=0.79 and p=0.4 respectively) (Table 2). Serum Ca and ALP levels prior to and after treatment have not shown any significant difference among the groups (p=0.4) (Table 3).

While uCA/Cr decreased significantly in etidronate group from 0.118±0.064 to 0.053±0.028 (p=0.004) and from 0.08±0.0 to 0.06±0.015 (p=0.005) in

Table 1. Age, parity, pregnancy rate and duration of menopause of patients (E: Etidronate, Pl: Placebo, E+Ca: Etidronate+Calcium).

	E	Pl	E+Ca	P	
Age	52.8±6.9	50.6±4.1	52±4.8	0.496	(NS)
Gravida	4.6±1.5	4.9±1.5	4.7±1.8	0.299	(NS)
Parity	4.2±1.4	4.4±1.1	4.3±0.7	0.32	(NS)
Duration of menopause	6.1±0.5	5.9±0.4	6.05±0.4	0.34	(NS)

* p > 0.05, ANOVA (NS): Not significant.

Table 2. E2, FSH, LH levels of groups.

	E	Pl	E+Ca	P	
E2 (pg/ml)	31.6±5.5	35.3±6.6	34.9±6.2	0.689	(NS)
FSH (mIU/ml)	66.7±7.3	68.6±5.6	70.3±6.8	0.79	(NS)
LH (mIU/ml)	82.8±10.1	79.5±6.7	78.4±8.4	0.4	(NS)

* p > 0.05, ANOVA (NS): Not significant.

Table 3. Serum Ca^{++} ad creatinin levels of groups prior to (P) and after (A) treatment.

		E	Pl	E+Ca	P
Serum Ca	P:	9.9±0.7*	9.69±0.6*	9.78±0.6*	0.4
(mg/dl)	A:	10.1±0.8^	9.7±0.7^	9.9±0.7^	
Serum ALP	P:	95±23.3*	90±16.7*	98.6±27.6*	0.4
(U/L)	A:	97±21.4^	93±18.3^	96±25.3^	

* p > 0.05, ANOVA ^ p> 0.05, Paired–t test.

etidronate+Calcium group, the drop in placebo group from 0.093±0.045 to 0.088±0.036 (p=0.3) was not significant following 3 months of treatment (Table 4).

During treatment no severe side effects were observed and no reason intervening with treatment has occurred in all groups. One patient, in each etidronate group, complained of nausea and diarrhea, and in the placebo group, two patients had nausea probably due to irritating effect of Fe on gastric mucosa.

Discussion

A large number of studies have shown the effectiveness of HRT in prevention of osteoporosis during menopause (4, 5) but its use is not without limitation due to associated risks (6). This knowledge led to alternative treatment modalities of osteoporosis in patients in whom HRT is contraindicated. In this point, biphosphonates have been used for osteoporosis since 1970's. The efficacy and safety of cyclical etidronate in reducing bone resorption through the inhibition of osteoclastic activity in osteoporosis is well established (12, 17, 18, 19, 20). However it seems that drug interferes with mineralisation of newly formed bone when given continuously, but this can be prevented by cyclical administration (12).

There are both histomorphometric and nonhistomorphometric studies confirming that etidronate reduces bone resorption. Although, in most of the refferences, dual energy x–ray absorpsiometry (DEXA) has been used in addition to nonhistomorphometric parameters for bone mineral density measurements, this histomorphometric tecnique costs relatively high. We do not argue that uCa/Cr is an alternative parameter to DEXA. Since uCa/Cr is a widely available measurement and very cheap, we decided to use uCa/Cr as a biochemical marker of bone turnover to show the effectiveness of etidronate and whether it could be used as a follow–up parameter of treatment. We found that etidronate is effective in postmenopausal women by decreasing bone resorption. We found that etidronate is effective in postmenopausal women by decreasing bone

Table 4. Urinary Calcium/Creatinin ratio of groups prior to (P) and after (A) treatment.

	Group	P	A	p	
E	(n:27)^	0.118±0.064	0.053±0.028	0.004	(S)
Pl	(n:27)	0.093±0.045	0.088±0.036	0.3	(NS)
E+Ca++	(n:27)^	0.08±0.030	0.06±0.015	0.005	(S)

^p < 0.05, Paired–t test (S): Significant (NS): Not significant.

resorption. In addition, the effectiveness of treatment may be followed up by simply measuring uCa/Cr. Smith et al. (21) have observed pre and post operative nonhistomorophometric parameters of bone turnover in intervals of 3 months in 20 healthy premenopausal and found that following 3 months of daily 400 mg editronate administration, the levels returned to premenopausal state. Reitsman et al. (22), by daily Pamidronate (biphosphanates) injections to rats, showed that suppression of both velocity and degree of bone resorption depends on dose regimen by measuring urinary hydroxyproline excretion. In our study, similar to the results by Smith et al. (21) in etidronate given groups uCa/Cr declined appreciably more than that in placebo group. That we have not documented any significant change in serum Ca levels (p=0.4) differs from the results by Smith et al. (21). Also the reported progressive increase in ALP levels in placebo group by these authors was not significant in our study (p=0.4).uCa/Cr in the placebo group was similar and no change in the ratio was observed after treatment (p=0.3).

Decline in uCa/Cr in this study was comparable to the results reported by some studies (23, 24, 25, 26, 27, 28). Contradiction to this finding is that some reports have shown no difference in uCa/Cr in patients treated with biphophonates (17, 18, 29, 30). This could be simply due to the drug used and/or the characteristics of population studied.

In this study, we concluded that etidronate is effective in postmenopausal women and the effectiveness of treatment may be followed up by measuring uCa/Cr which is a simple and cheap method of determining the effectiveness of treatment in prevention of osteoporosis. However, since there are contradictory findings concerning uCa/Cr exist, larger clinical and prospective studies should be carried out.

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