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Short-term Effects of Pamidronate on Biochemical Markers of Bone Metabolism in Osteoporosis— a Placebo-controlled Dose-finding Study

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ABSTRACT

The bisphosphonates are potent inhibitors of osteoclastic bone resorption that mainly have been used for treatment of hypercalcaemia secondary to malignancy. We have performed a controlled dose-finding study of oral pamidronate that was given to 60 patients with a history of fracture of the distal forearm, an enhanced bone turnover and a lowered bone mineral density.

Different doses of pamidronate, 75 mg and 150 mg daily, or placebo were given to parallel groups. Fasting specimens of blood and urine were collected before the treatment period and at regular intervals.

Oral pamidronate caused a dose-related reduction on the biochemical markers of bone resorption, i.e. fasting urinary calcium, hydroxyproline, pyridinoline and deoxypyridinoline that was seen already after the first week. The inhibition was evident during the treatment period and 4 weeks thereafter but not 12 weeks after cessation of therapy. Also the levels of serum osteocalcin, a marker of bone formation, were lowered during treatment with the higher dose.

INTRODUCTION

There is a great need of safe, inexpensive and effective treatments for osteoporosis. The bisphosphonates, potent inhibitors of osteoclastic activity (1), have been extensively used for treatment of hypercalcaemia associated with malignancy (4, 9, 19) and for primary and secondary prevention of osteolytic metastases (3, 13, 14). Their specificity for bone, low toxicity and great capacity to suppress bone resorption constitute properties that might make them suitable for prevention and treatment of osteoporosis. Recently, it has been reported that treatment with one bisphosphonate, etidronate, yielded a moderate increase in bone mass and some prevention of vertebral deformity (18, 21). Etidronate, however, has a narrow therapeutic range and might cause impaired mineralisation during long-term treatment (2, 12). Thus, other bisphosphonates might prove more valuable.

Pamidronate, 3-amino-1-hydroxypropylidene-1, 1-bisphosphonate, inhibits not only the osteoclastic activity but also the recruitment of osteoclasts from precursors (1, 17, 23). It therefore, appears to have a longer duration of action than other bisphosphonates but has previously mainly been available for parenteral use only. In the present study we have evaluated the biochemical responses to oral pamidronate during a 4-week placebo-controlled trial in patients with fractures of the distal forearm. Sensitive and specific markers for bone resorption and bone formation were utilized.

MATERIAL

Patients

From an ongoing prospective study of the epidemiology of distal forearm fractures (10) 60 patients were recruited. There were 51 postmenopausal women and 9 men (mean age 64.9 years, range 53-76 years) with a fracture within the last year but not within the preceding three months. They all had a bone mineral density (BMD) of the lumbar spine that was more than 1 SD below the reference range for young healthy individuals and a mean fasting urine calcium/creatinine above 0.20 mol/mol, indicating high bone turnover. Among the women none had been on estrogen therapy during the last year and menopause was more the 5 years ago. The patients had not taken any drugs known to influence bone metabolism, i.e. steroids, thiazides, fluorid, calcitonin, vitamin D or calcium supplements during the last year. No patient had had peptic ulcer and the patients were prohibited from taking any NSAID throughout the study.

Study protocol

The patients were randomized to a double-blind design treatment regimen, in blocks of 6, to 3 groups. Each patient was informed to take 2 capsules in the morning at least 30 minutes before breakfast for 28 days. The capsules contained either 75 mg sodium pamidronate in the form of enteric-coated pellets or inactive substance and were of identical shape and size. The three groups were provided with either 2 capsules of 75 mg pamidronate (150 mg), 1 capsule 75 mg pamidronate and 1 inactive capsule (75 mg) or 2 inactive capsules (placebo).

The patients were examined weekly during the 4 weeks of treatment and then after 4 and 12 weeks without medication. Morning urine samples were collected, after an overnight's fast, twice before the treatment period and after 1, 2, 3, 4, 8 and 16 weeks, while blood samples were collected only before and after 2 and 4 weeks of treatment.

Side effects were rated on a 3 pointed scale from mild over moderate to severe.

METHODS

Biochemical methods

Urinary hydroxyproline was measured by an amino acid analyzer and the values expressed as the hydroxyproline to creatinine ratio (U-OH-proline/creat). The measurements of the collagen crosslinks urinary pyridinoline and deoxypyridinoline were kindly performed by Professor Pierre D. Delmas, Lyon, France. The method (5) requires a purification step by cellulose chromatography of the hydrolyzed urine samples, separation by reversed phase HPLC, and identification by spectrofluorometry. Serum and urine calcium, serum alkaline phosphatase and albumin concentrations were analyzed by automated methods at the Department of Clinical Chemistry. Serum parathyroid hormone (PTH) was measured by a sandwich method that detects exclusively intact PTH (Allegro Intact PTH Immunoassay, Nicols Institute, San Juan Capistrano, CA, USA, normal range 10-55 ng/l). Serum osteocalcin was measured using a kit from CEA Oris, France, normal range 3-13 µg/l.

Statistical analysis

Treatment results were compared against each other using the time points after 4 weeks of active treatment as well as 4 and 8 weeks thereafter. This was done using an analysis of covariance with treatment as factor (class variable) and baseline (i.e. value at visit 1) as covariate. Using the baseline as covariate takes the differences between groups into account. All calculations were done with the SAS-software package using procedure GLM ("Generalized Linear Models").

The frequency of gastrointestinal complaints across the treatment groups were compared with the chi-square-test.

RESULTS

Both doses of pamidronate significantly reduced the biochemical indices of bone resorption, i.e. fasting urinary excretion of calcium, hydroxyproline and collagen crosslinks (Table 1).

This inhibition of bone resorption was evident already after the first week of therapy and persisted during the entire treatment period. For urinary calcium and hydroxyproline there were no differences between the 2 doses of pamidronate whereas there appeared to be a dose-dependent reaction for the urinary excretions of pyridinoline and deoxypyridinoline (Fig. 1). With regard to the indices of bone formation there was a reduction of serum osteocalcin concentrations during treatment with pamidronate but no significant change of serum alkaline phosphatases (Fig. 2). Serum calcium was slightly reduced and there was an increase of the serum PTH concentrations on the highest dose of pamidronate (Fig. 2).

The biomarkers of bone turnover had generally returned to pretreatment levels at the follow-up 12 weeks after cessation of therapy (Fig. 1).

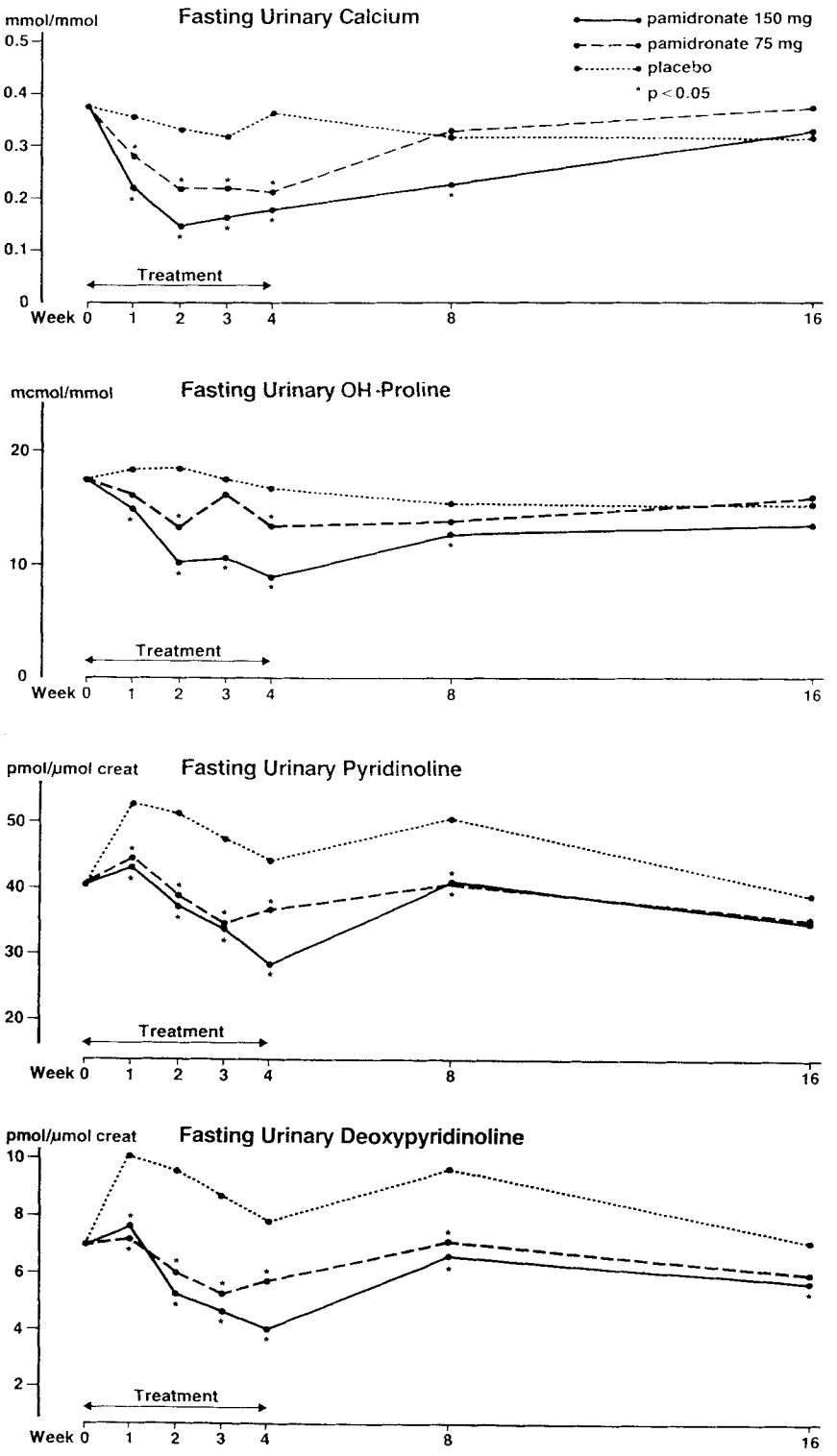

Figure 1 Effects of pamidronate and placebo on urinary excretions of markers for bone resorption

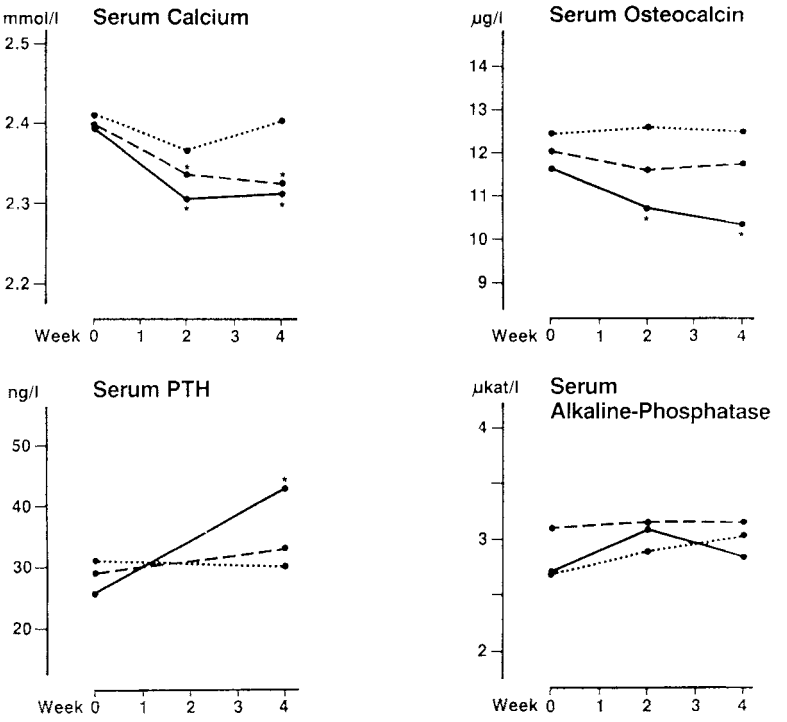

Figure 2 Effects of pamidronate (symbols as in Fig 1) on serum calcium, PTH and markers of bone formation

Table 1 Treatment contrasts for markers of bone resorption (p-values)

Fasting excretion of	Week 1	Week 2	Week 3	Week 4	Week 8	Week 16
Calcium						
150 mg vs placebo	.000	.000	.000	.000	.015	.736
75 mg vs placebo	.017	.005	.005	.001	.797	.171
150 mg vs 75 mg	.064	.072	.109	.445	.009	.305
Hydroxyproline						
150 mg vs placebo	.018	.000	.000	.000	.041	.206
75 mg vs placebo	.114	.001	.457	.005	.218	.678
150 mg vs 75 mg	.408	.036	.002	.000	.411	.095
Pyridinoline						
150 mg vs placebo	.011	.000	.001	.000	.013	.116
75 mg vs placebo	.021	.000	.001	.027	.009	.173
150 mg vs 75 mg	.742	.611	.873	.017	.922	.817
Deoxypyridinoline						
150 mg vs placebo	.006	.000	.000	.000	.000	.018
75 mg vs placebo	.001	.000	.000	.002	.003	.056
150 mg vs 75 mg	.592	.366	.472	.016	.530	.634

Pamidronate was usually well tolerated without changes of pulse rates and blood pressure. Some gastrointestinal complaints were reported with 32 events for the 150 mg dose, 24 on 75 mg and 12 on placebo but with a reduction in frequencies during the treatment period. There was no

significant relation of severity of gastrointestinal disorders to the different treatment groups. The overall assessment of tolerabililty, estimated at visit 5 (after 4 weeks of treatment), was good or excellent in at least 90%, for all groups (Table 2).

Table 2 Overall assessment of tolerability after 4 weeks of treatment

	Excellent	Good	Moderate	Poor	Total
Placebo	17	1	1	1	20
75 mg pamidronate	16	3	0	1	20
150 mg pamidronate	10	8	1	1	20
Total	43	12	2	3	60

DISCUSSION

The findings of the present study of one-month therapy demonstrate that pamidronate effectively inhibited bone resorption in a dose dependent manner. Three months after cessation of treatment most indices of bone turnover had returned to the pretreatment level.

It is known for bisphosphonates that they have a long half-life in the skeleton (7, 11, 19). In clinical trials with bisphosphonates attempts have therefore been made with cyclic treatment in order to avoid complete inhibition of bone resorption and subsequent restraint of bone formation and remodelling (18, 21). The findings of the present study indicate that oral pamidronate 150 mg daily for 1 month out of 4, is to be preferred if an intermittent, cyclic, regimen is to be applied.

Beside the expected reduction of all indices of bone resorption there was also in the present investigation an increase of serum PTH during active treatment. This was presumably related to the concomitant reduction of serum calcium, another consequence of osteoclastic inhibition. Stimulation of PTH was not described in the studies with etidronate but might be of additional value since PTH has an anabolic effect and intermittent doses of PTH have been tried as a treatment for osteoporosis (20). A direct effect of PTH with a decrease of serum osteocalcin has been observed during short-term infusions of the hormone (8) and might explain the dissociate responses of osteocalcin and serum alkaline phosphatases.

Pamidronate, a third generation of bisphosphonates, has previously mainly been used for treatment of malignancy-related hypercalcemia and osteolytic metastases and only few accounts have been concerned with treatment of osteoporosis. In one short report it was described that bone mass was preserved in patients on chronic corticosteroid treatment who in addition received oral pamidronate continuously for 2 years (22). It has also been reported that pamidronate administration increased bone mass, measured as total body calcium (20) in patients with osteoporosis treated during 3.7 years.

In conclusion, the results from this short-time study of biomarkers for bone demonstrate properties of pamidronate which might be useful in prevention and treatment of high turnover osteoporosis.

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