THE USE OF CYCLICAL ETIDRONATE IN OSTEOPOROSIS: CHANGES AFTER COMPLETION OF 3 YEARS TREATMENT

A. FAIRNEY, P. KYD,* E. THOMAS* and J. WILSON*

Imperial College School of Medicine at St Mary's, Norfolk Place, London W2 1PG and *St Mary's NHS Trust, Paddington, London W2 1PG

SUMMARY

An open study over 4 yr has been conducted to determine the efficacy of cyclical etidronate treatment in patients from the community, with osteoporosis and in those at risk who attended an osteoporosis clinic; and to clarify whether bone remodel-ling returns to baseline values and bone mass is maintained after completion of a 3 yr course of treatment. One hundred and fifteen female patients, with and without osteoporotic fractures (n = 62 and 53, respectively), who were unsuitable for, or declined, hormone replacement therapy, received 3 yr cyclical etidronate treatment (400 mg etidronate disodium for 14 days followed by 500 mg elemental calcium for 76 days repeated in 3-monthly cycles) and 1 yr treatment-free follow-up. There was an overall increase in lumbar spine bone density (patients without fractures 2.6%, P < 0.001; with fractures 4.3%, P < 0.01) with minimal change at the femoral neck. The serum concentration of bone formation markers (osteocalcin and bone alkaline phosphatase) fell in response to treatment to a nadir at 6/12 (75 and 83% of baseline, respectively; P < 0.001). A cohort of patients (n = 29), 14 without fractures and 15 with fractures, was studied in more detail. After completion of treatment in the following treatment-free year, there was a resurgence of bone turnover (osteocalcin and bone alkaline phosphatase 117 and 122% of baseline, respectively; P < 0.05 and P < 0.01) with some evidence of maintenance of bone mass already gained. There is no evidence of persistent suppression of bone turnover after completion of treatment.

Key words: Cyclical etidronate, Osteoporosis, Bone density, Bone cell markers, Completion of treatment.

POST-MENOPAUSAL women with osteoporosis, and those identified by bone densitometry as being at risk of osteoporosis, are usually offered hormone replacement therapy (HRT) as first-line therapy or prophylaxis. However, a significant number of these patients are not suitable for, or do not wish to have, HRT and are keen to have some alternative form of treatment. Intermittent cyclical treatment with the bisphosphonate etidronate has been shown to be a suitable alternative [1,2].

In the UK, until recently, this treatment has been provided as a 3 yr course of Didronel PMO (Procter and Gamble) for established vertebral osteoporosis. There is now evidence that 7 yr of this treatment increases and maintains bone mass, without evidence of significant side-effects such as osteomalacia [3–5]. However, it is unclear whether this treatment is suitable for patients at risk of osteoporosis without fractures, and also whether the increase in bone mass is maintained after completion of the present recommended 3 yr course of Didronel.

We have undertaken an open study on patients with osteoporotic vertebral fractures and those at risk of osteoporosis who were referred to our clinic, paying particular attention to the biochemical and bone density changes after completion of 3 yr cyclical etidronate treatment.

The aims of the study were: (a) to determine whether patients with low bone density, with or without osteoporotic fractures, responded to cyclical etidronate treatment with an increased bone mass, as has previously been documented; (b) to determine whether patients who have had a 3 yr course of this treatment lose the bone they have gained on completion of the treatment during the post-treatment year; (c) to determine whether the suppressed bone remodelling returns to baseline after the completion of treatment.

SUBJECTS AND METHODS

Female patients, referred to the St Mary's osteoporosis clinic, requiring treatment to prevent further bone loss were studied. After initial assessment by bone densitometry, patients who did not wish to have HRT, or in whom it was contraindicated, were offered cyclical etidronate therapy. Patients included either had obvious radiological evidence of osteoporosis with vertebral wedging and fractures, or had bone density values in the lumbar spine < 2 s.d. below the young adult reference mean (Y.A.Z. score, equivalent to T score < −2).

One hundred and fifteen patients were treated with 400 mg etidronate disodium (Didronel; Procter and Gamble Pharmaceuticals) for 14 days, followed by 500 mg elemental calcium (1250 mg calcium carbonate) (Cacit; Procter and Gamble Pharmaceuticals) for 76 days in 3-monthly cycles. The patients were counselled about the importance of taking etidronate on an empty stomach, at least 2 h before or 2 h after eating. One hundred and four of these patients have been followed up for 1 yr (Group 1, 53 without fractures; Group 2, 14 with steroid-induced osteoporosis, 29 with fractures).

Submitted 31 December 1996; revised version accepted 9 June 1997.
Correspondence to: A. Fairney.

© 1998 British Society for Rheumatology
all of whom had fractures and who were taking corticosteroids as suppressed therapy; Group 3, 48 with osteoporosis and fractures) and 85 patients have been followed up for 2 yr (37, 12 and 36 in Groups 1, 2 and 3, respectively). Ten of the Group 2 patients were taking prednisolone in doses ranging from 1 to 15 mg/day, two patients were taking hydrocortisone and the final two patients were taking intermittent prednisolone together with inhaled steroids. Baseline characteristics of the patients studied are presented in Table I. A cohort of 29 of the patients completing 2 yr of treatment was studied in more detail during the third year of treatment and during the first year after completion of treatment. Of these 29 patients, 14 did not have fractures, originated from Group 1 and are described as Group 4; 15 patients had osteoporosis with fractures, originated from Groups 2 and 3, and are described as Group 5 (four of this group were taking corticosteroids) (see Table II).

Bone densitometry (BMD) of the spine (L2–L4) and femoral neck (LUNAR DXA, Madison, USA) was measured before and at annual intervals after commencing treatment (precision for normal subjects: L2–L4 1%; femoral neck 2%). When fractures or deformities were present in the L2–L4 region, those vertebrae were excluded from the analysis. Also, all vertebrae where the area had changed by a reduction of $\geq 10\%$ were excluded from the analysis, so that any increase in bone density due to collapse or deformity was eliminated from the results reported.

Patients were followed at 3-monthly intervals, at which time general biochemistry tests were performed by standard autoanalyser techniques [Olympus AU5200, Olympus Optical Co. (UK) Ltd, Eastleigh]; intact parathyroid hormone (PTH) by IRMA (Nichols Institute Diagnostics Ltd, Safron Waldon), within-batch coefficient of variation (CV) <3%, between-batch <6%; osteocalcin by radioimmuno-assay [OSTK-PR RIA; CIS (UK) Ltd, High Wycombe], within-batch CV <3%, between-batch <6%; and bone-specific alkaline phosphatase by IRMA (Tandem Ostase TM, Hybritech, San Diego, CA, USA), within-batch CV <3%, between-batch <8%. Samples for bone-specific alkaline phosphatase were stored at $-20^\circ$C and analysed in a single batch. Samples for osteocalcin (which is not stable when frozen for long periods), PTH and general biochemistry were analysed as collected during the study. Daily calcium intake was assessed by means of a dietary questionnaire.

### Statistical analysis
The primary analysis concerned the bone density measurements and comparisons were made on a within-patient basis separately for each of the patient groups. The paired $t$-test was used to compare base-

<table>
<thead>
<tr>
<th>Group</th>
<th>Years of treatment</th>
<th>n</th>
<th>Baseline g/cm²</th>
<th>Post-dose g/cm²</th>
<th>% change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 No fractures</td>
<td>1</td>
<td>47</td>
<td>0.790 (0.10)</td>
<td>0.805 (0.11)</td>
<td>1.9</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>34</td>
<td>0.798 (0.12)</td>
<td>0.819 (0.12)</td>
<td>2.6</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>2 Steroids</td>
<td>1</td>
<td>13</td>
<td>0.823 (0.12)</td>
<td>0.850 (0.14)</td>
<td>3.2</td>
<td>NS</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>12</td>
<td>0.802 (0.10)</td>
<td>0.844 (0.14)</td>
<td>5.2</td>
<td>NS</td>
</tr>
<tr>
<td>3 Fractures</td>
<td>1</td>
<td>41</td>
<td>0.820 (0.12)</td>
<td>0.845 (0.13)</td>
<td>3.0</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>36</td>
<td>0.822 (0.11)</td>
<td>0.857 (0.13)</td>
<td>4.3</td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td>4 No fractures</td>
<td>1</td>
<td>14</td>
<td>0.814 (0.08)</td>
<td>0.839 (0.1)</td>
<td>3.0</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Change in treatment-free year</td>
<td>14</td>
<td>0.839 (0.1)</td>
<td>0.827 (0.1)</td>
<td>$-1.5$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Fractures and steroids</td>
<td>1</td>
<td>15</td>
<td>0.823 (0.13)</td>
<td>0.857 (0.15)</td>
<td>4.1</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>Change in treatment-free year</td>
<td>15</td>
<td>0.857 (0.15)</td>
<td>0.872 (0.15)</td>
<td>1.8</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>
line with yr 1 values and baseline with yr 2 values. The results were summarized by means and S.D. at each time point for those patients who had paired data, plus the percentage change from baseline, mean difference, standard error of difference, t-test statistic, degrees of freedom and P value.

The secondary variables were the background details and biochemical markers. The background details were summarized for each group using means, S.D., median and range or frequencies within each category as appropriate to the data. Biochemical markers were summarized by means of S.E.M. at each 3-monthly time point.

RESULTS

Changes in spine BMD over 2 yr of treatment are shown in Table II and over the first 2 yr of treatment there was a significant increase in density ranging from 2.6% in patients without fractures (Group 1) to 4.3% in patients with fractures (Group 3) and 5.2% in patients on steroids (Group 2). The changes in BMD were not significantly different between the groups, but were significantly different individually when compared to baseline. Slight increases were observed in the femoral neck, especially in Group 1 patients, but these were too small and the variability too large to be statistically significant. The concurrent changes in the biochemical analyses are shown in Table III.

The changes in the spine and femoral neck bone density for the cohort of 29 patients, Groups 4 and 5, are shown in Figs 1 and 2. The changes in the treatment-free year (fourth year) did not reach statistical significance, but the data suggest that these patients without fractures lost bone more readily than those with fractures. In the overall cohort, eight patients had a significant decrease in lumbar spine bone density (Fig. 3) and 13 patients had a significant decrease in femoral neck bone density. However, there were 12 patients who showed a significant increase in lumbar spine bone density. The results did not correlate with the age of the patients. The mean changes in bone alkaline phosphatase and osteocalcin in the 25 of these patients who were fully evaluated are shown in Table III and Fig. 4. There is a signific-

![Graph showing changes in lumbar spine BMD](image1)

![Graph showing changes in femoral neck BMD](image2)

FAIRNEY ET AL.: ETIDRONATE IN OSTEOPOROSIS 53

<table>
<thead>
<tr>
<th>Time after start of treatment</th>
<th>Osteocalcin μg/l (1.0–12.5)</th>
<th>Bone ALP μg/l (3–21.5)</th>
<th>Total ALP U/l (30–130)</th>
<th>PTH ng/l (10–65)</th>
<th>Calcium mmol/l (2.15–2.55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.1 (0.6)</td>
<td>11.8 (0.9)</td>
<td>83 (3)</td>
<td>36 (3)</td>
<td>2.28 (0.02)</td>
</tr>
<tr>
<td>0.5 yr</td>
<td>6.1 (0.6)**</td>
<td>9.8 (0.7)**</td>
<td>72 (4)*</td>
<td>34 (5)</td>
<td>3.13 (0.02)</td>
</tr>
<tr>
<td>1 yr</td>
<td>6.6 (0.5)**</td>
<td>9.4 (0.6)**</td>
<td>76 (4)*</td>
<td>37 (5)</td>
<td>2.28 (0.02)</td>
</tr>
<tr>
<td>2 yr</td>
<td>6.2 (0.4)**</td>
<td>11.8 (1.1)</td>
<td>90 (2)</td>
<td>34 (2)</td>
<td>2.30 (0.02)</td>
</tr>
<tr>
<td>3 yr</td>
<td>6.7 (0.5)*</td>
<td>11.8 (1.0)</td>
<td>85 (4)</td>
<td>39 (3)</td>
<td>2.32 (0.03)</td>
</tr>
<tr>
<td>1 yr off treatment</td>
<td>9.5 (0.6)**</td>
<td>14.5 (1.0)**</td>
<td>86 (4)</td>
<td>42 (6)</td>
<td>2.27 (0.02)</td>
</tr>
</tbody>
</table>

n = 25, mean (S.E.M.).
Statistics: paired t-test compared with baseline.
*P < 0.05; **P < 0.01; ***P < 0.002.
ant decrease in bone alkaline phosphatase and osteocalcin after the start of treatment, which is maximal at 6 months, and a significant rise above baseline in these bone markers after the etidronate treatment has been discontinued.

There were no significant changes in serum calcium or PTH during the 4 yr of the study in any of the patients, and the bone marker values did not correlate with changes in bone density. Also, the dramatic changes seen in the treatment-free year did not correlate with or predict the rise or fall in bone density.

Etidronate was in general well tolerated with no serious adverse events. However, out of a total of 115 patients treated, five developed mild skin rashes and four patients had gastrointestinal symptoms, e.g. diarrhoea. These symptoms may have been related to the calcium carbonate given as part of the cyclical regime, and 16 patients changed from the effervescent calcium carbonate supplement onto a chewable form of calcium carbonate. All patients accepted the need to take the etidronate in the fasting state. However, one patient developed panic attacks, and another mood swings similar to pre-menstrual tension, in relation to the 14 days of etidronate in each 3-month cycle.

**DISCUSSION**

HRT is well recognized as an important agent in the prevention and treatment of osteoporosis [6]. In the UK, compliance with long-term treatment is often poor, and patients may be reluctant to take agents which prolong menstruation. In addition, HRT is contraindicated in patients with breast cancer, and patients are anxious about the possible association of HRT and an increased risk of developing breast carcinoma, in spite of potential long-term benefits preventing cardiovascular disease or the onset of dementia.

There is, therefore, a need for non-hormonal treatments to prevent and treat osteoporosis. Bisphosphonates, especially etidronate, have been developed for this purpose. Intermittent cyclical etidronate therapy, using disodium ethane-1-hydroxy-1,1-bisphosphonate for 2 weeks in every 12 weeks, significantly increases spinal bone mass and reduces the incidence of new vertebral fractures [1, 2]. Until recently, this treatment has only been licensed in the UK for 3 yr, although further studies have shown that continuation of the treatment for up to 7 yr [3, 5] increases bone mass, is safe, well tolerated and does not cause osteomalacia. However, there is still concern amongst physicians regarding the efficacy of this treatment, how long it should be used for, what happens to the bone when a course of treatment is completed and whether this drug produces long-standing suppression of bone remodelling.

The study described here confirms that cyclical etidronate treatment (given as Didronel PMO, Procter and Gamble Pharmaceuticals) produces a significant increase in lumbar spine bone density, is safe to prescribe and in general is well tolerated by patients. This therapy produced very little change in femoral neck bone density and, as expected, was accompanied by suppression of osteoblast biochemical markers. This reflected decreased bone turnover and was maximal at 6 months. Unfortunately, we did not have access to measurements of bone resorption markers such as pyridinium cross-links at the start of this study. Also, we did not have a control group of patients as it was not considered ethical to leave some patients with osteoporosis attending the clinic without treatment.

After completion of treatment, there was a striking rise in bone alkaline phosphatase and osteocalcin to supra-baseline values. The patients did not receive...
any other treatment, such as calcium and vitamin D, during the treatment-free year; some patients maintained and even increased their bone density. The increase in bone turnover is unlikely to be due to a lack of calcium or vitamin D, since there was no change in plasma calcium or PTH. There was no statistical relationship between changes in bone density and bone cell markers. There is no obvious explanation for the increased bone mass in some of the patients. Because many of these patients remained with significant bone loss, they were subsequently given a further course of etidronate or changed to another bisphosphonate. This prevented the opportunity to observe the change in bone density for a second treatment-free year.

The patients who lost bone density during the treatment-free year have given cause for concern. Continuous use of etidronate at higher doses in Paget’s disease may cause osteomalacia [7, 8]. However, more recent bone histomorphometric studies after cyclical therapy with disodium etidronate in women with post-menopausal osteoporosis did not show evidence of osteomalacia [9]. In our patients, although there was a rise in bone alkaline phosphatase after treatment, which would be compatible with biochemical osteomalacia, the serum calcium and PTH values remained completely normal.

The loss of bone occurring in some of our patients after completion of etidronate treatment may be similar to that observed after completion of HRT. Heaney [10] predicted, using a quantitative model of involutional bone loss, that oestrogen replacement therapy, if stopped, does not produce a sustained difference in bone mass in calcium-replete women. He hypothesized that 10–15% of skeletal mass is oestrogen dependent. This amount of bone is lost rapidly soon after the menopause when oestrogen is not taken or is lost rapidly later in life when oestrogen treatment is stopped. In the Framingham study [11], only women who had taken oestrogen for 7 or more years had higher bone density than those who had never taken oestrogen treatment, and even this duration of treatment had little effect on bone density among women of 75 yr and older.

The bisphosphonates are now accepted as an important group of therapeutic compounds for use in the treatment of osteoporosis, Paget’s disease and metastatic bone disease. Their mechanism of action has recently been reviewed by Rodan and Fleisch [14]. They produce decreased bone turnover resulting from decreased bone resorption which relates to inhibition of osteoclast recruitment and osteoclast activity, as well as alteration of bone mineral. The P-C-P group of the bisphosphonate molecule is resistant to enzymatic hydrolysis, so these compounds are not metabolized in the body and are excreted unchanged. The concern about continued suppression of bone remodelling due to retention of bisphosphonates in bone seems to be ill-founded. However, the bisphosphonates are released from bone during bone remodelling and might be pharmacologically active.

This may explain why in some patients treated with bisphosphonates the improved bone density is maintained or even improved. Osteoblasts, when exposed to low concentrations of potent bisphosphonates such as alendronate, produce an inhibitor which reduces bone resorption, by affecting osteoclast recruitment or survival [15]. Therefore, in addition to the role of osteoblasts in governing physiological osteoclastic bone resorption, the osteoblast seems to act in response to bisphosphonates in a paracrine fashion to inhibit bone loss. This may also explain the maintenance of bone mass after completion of treatment with bisphosphonates.

The changes in bone turnover after completion of treatment in our patients are in agreement with those described after discontinuation of pamidronate [12]. Pamidronate, an aminobisphosphonate, 150 mg/day, given for 6 yr, produced 10% suppression of total serum alkaline phosphatase which returned to baseline values 6 months after completion of treatment. However, there was no evidence of a rebound phenomenon in bone turnover and bone density was maintained at the post-treatment level for 2 yr. With alendronate, another amino bisphosphonate recently licensed as Fosamax (Merck, Sharp and Dohme) for the treatment of osteoporosis, values of bone alkaline phosphatase return to baseline after 6 months off treatment [13].

Our study shows more dramatic changes in bone cell markers than those seen with pamidronate. This may be due to the use of more specific osteoblast markers and also the different type of bisphosphonate prescribed. Cessation of etidronate treatment may be followed by loss of inhibition of osteoclast recruitment and activation.

We conclude that the bisphosphonate etidronate is safe to use in osteoporosis and is well tolerated. There is no evidence that prolonged suppression of bone remodelling is produced after completion of treatment. Some patients maintain or even increase their bone mass after etidronate. This may be due to continued slow release of the bisphosphonate from bone. Intermittent courses of bisphosphonates in osteoporosis may be more successful than continuous treatment for many years.

Acknowledgements

We wish to thank Miss Katherine Isaac for bone alkaline phosphatase measurements, Miss Margaret Murphy for bone density measurements and Jill Altman for undertaking statistical analysis.

References


