Long Term Efficacy of Cyclical Etidronate Therapy in Postmenopausal Osteoporosis

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Abstract
Sixty-two women (mean age 68.7 ± 0.9 yr) with postmenopausal spinal osteoporosis were treated with cyclical etidronate therapy (400 mg for 2 weeks alternating with 12 weeks of 1 gm elemental calcium and 400 IU Vitamin D3) for a minimum of 2 yr. Bone mineral density (BMD) of the lumbar spine (g/cm²) increased significantly (p<0.0001) after yr 1 (4.1 ± 0.5 per cent) and yr 2 compared with yr 1 (2.2 ± 0.5 per cent). The response rate was 89 per cent after yr 1 and 84 per cent after yr 2.

BMD of the hip (30 patients) increased by 1.5 ± 0.9 per cent after yr 1 and 5.5 ± 1.1 per cent (p<0.0001) after yr 2 when compared with baseline. The response rate was 63 per cent after yr 1 and 80 per cent after yr 2. Smaller numbers of patients continued with treatment up to 4 yr with no adverse long-term effects.

Introduction
Since the publication of the two original papers\textsuperscript{1,2} in 1990 showing the efficacy of cyclical etidronate therapy in increasing bone mass and reducing spinal fracture incidence, this treatment has become established as the mainstay in therapy for postmenopausal osteoporosis.

It is perhaps surprising that there have been relatively few studies published subsequently assessing the efficacy of this regime in a clinical setting. It is also important to establish whether similar findings are applicable to a United Kingdom population.

We report our experience with long term cyclical etidronate therapy in postmenopausal osteoporosis in relation to its effect on bone mineral density (BMD) and vertebral fracture.

Methods
Patients
From a computerised record of patients attending our Regional Osteoporosis Clinic over the past 5 yr, we have retrospectively identified 62 postmenopausal women with spinal osteoporosis who had received a minimum of 2 yr treatment with cyclical etidronate, (mean age 68.7 ± 0.9 yr, range 54-82 yr). Spinal osteoporosis was defined as a minimum of 1 low trauma vertebral fracture having excluded secondary causes of vertebral fracture. Disodium etidronate 400 mg/day was taken for 2 weeks, followed by 1g elemental calcium with 400 iu vitamin D3 for 12 weeks. The cycle was then repeated continuously. The etidronate was taken prior to bedtime following a 2 hr fast and calcium/vitamin D3 taken with meals.

Bone Mineral Density
BMD was measured prior to the start of therapy and annually thereafter. BMD (g/cm²) of lumbar spine (L1-L4) and total hip were measured by Dual Energy X-ray Absorptiometry (Hologic QDR-1000). The coefficient of variance of the spine was 0.3 per cent, within patient coefficient of variance was 1.07 per cent for the spine and 2.1 per cent for the hip. Lateral X-rays of thoraco-lumbar spine were obtained in a subgroup of patients at baseline and at yr 2. A vertebral fracture was defined as a reduction of 20 per cent or more in the anterior, middle or posterior vertebral height. If a further deformity occurred at the same vertebra, a new vertebral fracture was defined as a further reduction of 20 per cent in the anterior, middle or posterior vertebral height.

Statistical Methods
The percentage change in BMD was calculated for each patient and then these values used to determine the mean and standard error for the group. BMD was compared at the end of each year with the baseline measurement and for yrs 2, 3 and 4 with the previous year. Comparison was made with paired t-test. All patients were included in the analysis of change in BMD in yrs 1 and 2. When analysing the change in BMD in yrs 3 and 4, patients whose medication had been discontinued did not form part of the analysis. The number of vertebral fractures at baseline and yr 2 was also analysed using paired t-test. A level of significance was set at p value < 0.05.

Results
Sixty-two patients completed 2 yr of cyclical etidronate therapy. One patient discontinued therapy at yr 2 due to nausea. Therapy was discontinued in 10 patients at yr 2 due to a decrease in BMD. Thirty-two patients completed 3 yr of therapy, the remaining patients have yet to complete 3 yr of treatment (n=19). Nine patients have completed 4 yr of treatment to date. BMD of spine was significantly increased throughout all yrs of treatment when compared to baseline (p<0.0001) for yrs 1, 2 and 3, p<0.005 for yr
TABLE I
SPINE BMD RESPONSE TO CYCLICAL ETIDRONATE THERAPY

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Year</th>
<th>mean BMD (g/cm²) ± SE</th>
<th>mean (%) change ± SE compared with baseline</th>
<th>mean (%) change ± SE compared with previous year</th>
</tr>
</thead>
<tbody>
<tr>
<td>62</td>
<td>baseline</td>
<td>0.647 ± 0.014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>62</td>
<td>1</td>
<td>0.672 ± 0.014**†</td>
<td>4.1 ± 0.5</td>
<td>4.1 ± 0.5</td>
</tr>
<tr>
<td>62</td>
<td>2</td>
<td>0.686 ± 0.015**†</td>
<td>6.3 ± 0.7</td>
<td>2.2 ± 0.5</td>
</tr>
<tr>
<td>32</td>
<td>3</td>
<td>0.676 ± 0.014**</td>
<td>7.6 ± 1.0</td>
<td>0.2 ± 0.7</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>0.653 ± 0.033*</td>
<td>7.0 ± 1.6</td>
<td>-1.9 ± 1.0</td>
</tr>
</tbody>
</table>

*(p<0.005) compared with baseline
** (p<0.0001) compared with baseline
† (p<0.0001) compared with previous year

4). BMD of spine was significantly increased at yr 2 when compared to yr 1 (p<0.0001), but not in yrs 3 and 4 when compared to the previous yr. The mean percentage change in BMD was greatest in year one. The BMD showed little change in the third and fourth years (Table I).

Thirty-seven patients had radiographs at baseline and after 2 yr treatment. This subgroup was not significantly different to the whole patient group with regard to age, baseline BMD and vertebral fracture rate. Two patients developed 1 new vertebral fracture each during this time period.

In 30 patients hip BMD was also measured after 1 and 2 yr of therapy. In 4 patients therapy was discontinued at yr 2 due to a decrease in BMD. Sixteen patients had hip BMD measured at yr 3. The remaining patients have yet to complete 3 yr of treatment (n=10). Eight patients have completed 4 yr of treatment to date. BMD of total hip was not significantly increased at yr 1 but significantly increased at yrs 2, 3 and 4 when compared with baseline (p values of <0.0001, <0.01 and. <0.05 respectively). BMD of total hip was significantly increased in yr 2 compared with yr 1 (p<0.0001) but not when other yrs were compared with the previous yr. Mean percentage increase in total hip BMD showed a different pattern to spine BMD as the largest increase was not in the first yr but the second (Table II).

At year two 80 per cent of patients showed an increase in hip BMD and 84 per cent an increase in spine BMD when compared with baseline.

TABLE II
HIP BMD RESPONSE TO CYCLICAL ETIDRONATE THERAPY

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Year</th>
<th>mean BMD (g/cm²) ± SE</th>
<th>mean (%) change ± SE compared with baseline</th>
<th>mean (%) change ± SE compared with previous year</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>baseline</td>
<td>0.601 ± 0.021</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>1</td>
<td>0.609 ± 0.021</td>
<td>1.5 ± 0.9</td>
<td>1.5 ± 0.9</td>
</tr>
<tr>
<td>30</td>
<td>2</td>
<td>0.632 ± 0.022***†</td>
<td>5.5 ± 1.1</td>
<td>3.9 ± 0.8</td>
</tr>
<tr>
<td>16</td>
<td>3</td>
<td>0.640 ± 0.029**</td>
<td>3.7 ± 1.1</td>
<td>-0.2 ± 0.9</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>0.625 ± 0.039*</td>
<td>6.1 ± 1.9</td>
<td>0.3 ± 1.3</td>
</tr>
</tbody>
</table>

*(p<0.05) compared with baseline
** (p<0.01) compared with baseline
*** (p<0.0001) compared with baseline
† (0<0.0001) compared with previous year

Discussion

Subjects in clinical trials are usually well motivated and are often healthier individuals than those subsequently given the drug in clinical practice. It is thus reassuring that we have found cyclical etidronate therapy to be so well tolerated. While a small number of subjects dropped out after a few weeks of treatment, only one subject out of 62 discontinued therapy after yr 1 because of nausea. Patients are often willing to tolerate such symptoms as they know that they only have to take the etidronate for 2 weeks out of every 3 months.

We have used a combination of 1g calcium plus 400 IU vitamin D3 in the chewable form. This has been well tolerated by most patients. The vitamin D may also enhance calcium absorption in a predominantly older population, many of whom have reduced calcium absorption. A similar dose of vitamin D was given to Storm's patients but none was used in the Watts study.

BMD of spine was significantly increased at all yrs when compared to baseline. The increases seen in yrs 1 and 2 (4.1 per cent and 6.3 per cent respectively) compare favourably with that of other studies - Watt et al (4.9 per cent at yr 2) and Storm et al (5.35 per cent at yr 3). The group of patients who responded to treatment with increased BMD continued on therapy for a third and fourth yr and maintained this increase in spine BMD (7.6 per cent and 7 per cent respectively), but did not show any further significant increase in BMD. This is similar to results shown by Harris et al where spine BMD increased.