Effect of intermittent cyclical disodium etidronate therapy on bone mineral density in men with vertebral fractures

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Abstract

Objectives: to investigate the effects of oral intermittent cyclical etidronate therapy on bone mineral density (BMD) in men with idiopathic vertebral osteoporosis.

Design: consecutive case series.

Setting: regional specialist clinic for metabolic bone disease.

Subjects: 42 men aged 35–81 (median 60.5) with established vertebral crush fractures and back pain, in whom secondary causes of osteoporosis had been excluded.

Intervention: repeated cycles of treatment with oral disodium etidronate 400 mg daily for 14 days followed by oral calcium 500 mg as citrate daily for 76 days.

Outcome measures: BMD measurement of the lumbar spine and femoral neck by dual energy x-ray absorptiometry at 6–12-month intervals; bone biochemistry (serum calcium, phosphate, alkaline phosphatase and urine calcium/creatinine and hydroxyproline/creatinine ratios) at 6-month intervals.

Results: all 42 men have been treated for more than 18 months, and 35 of them for more than 24 months. Median follow-up for the group as a whole is 31 months (range 18–45). The treatment was well tolerated. BMD at the lumbar spine increased by a mean of 0.024 g/cm² per year of follow-up (95% confidence interval 0.017–0.032 g/cm²). This is equivalent to an average annual rate of change of 3.2% of baseline values. There was a small, non-significant rise in mean BMD at the hip equivalent to 0.7% of baseline values per year. Serum alkaline phosphatase tended to fall in the first 6 months of treatment, returning to baseline values at 2 years. Serum calcium and phosphate were unchanged and no decrease in urinary calcium/creatinine ratio or hydroxyproline/creatinine ratio was seen.

Conclusions: intermittent cyclical etidronate therapy increased lumbar spine BMD over a 2-year period in an unselected group of men with osteoporotic vertebral fractures. This treatment warrants further evaluation in a randomized controlled trial.

Keywords: bone mineral density, etidronate, male, osteoporosis, vertebral fracture

Introduction

More than 10% of Caucasian men who reach the age of 50 will experience an osteoporosis-related fracture before they die [1] and there is a high mortality in those who sustain such fractures [2, 3]. For survivors, pain and disability are likely to persist, impairing their quality of life, imposing substantial burdens on their carers and having financial implications for health and social services [3, 4]. The incidence of osteoporotic fracture in men is rising, in part due to population ageing, but also due to a poorly understood increase in age-specific incidence [5–7]. As awareness increases of how common the condition is in men, there may also be increased ascertainment, particularly of vertebral fractures.

The treatment of male osteoporosis has been the subject of much less research than treatment of women and there is no consensus on an appropriate choice of therapy [8]. Bisphosphonates are synthetic analogues...
of inorganic pyrophosphate which have been found useful in the management of disorders of increased bone turnover. Disodium etidronate (1-hydroxyethylidene-1,1-bisphosphonate) was the first of these compounds to be introduced for clinical use and there is extensive research evidence and clinical data on its use in patients with osteoporosis [9, 10]. In continuous use it can impair the mineralization of new bone, resulting in accumulation of osteoid and loss of bone strength. Intermittent cyclical disodium etidronate therapy (ICDT) was developed in response to this problem: it consists of short courses of disodium etidronate, usually 14 or 15 days, separated by approximately 3 months of either calcium supplementation or no treatment. Resorption is suppressed while impairment of bone mineralization is minimized [11].

The use of this treatment in women with established vertebral osteoporosis is based on the studies conducted by Storm [12] and Watts et al. [13,14] following Anderson's preliminary work [11]. In men, attention has focused on those with secondary osteoporosis, particularly in corticosteroid-treated patients. In both sexes ICDT prevents bone loss associated with continuing steroid therapy [15], and this approach has been endorsed by a recent consensus conference [16]. One study reported an increase in lumbar spine BMD in osteoporotic men treated with etidronate, although this involved patients with both primary and secondary osteoporosis and the analysis involved pooling the results of two groups treated with different cyclical regimens [17]. We began using ICDT in male patients with idiopathic osteoporosis in 1991 and report our experience to date.

Methods
Subjects
All men referred to the Newcastle upon Tyne bone clinic with possible osteoporosis were investigated according to our standard protocol [18]. This includes bone mineral density (BMD) measurement by dual energy x-ray absorptiometry, investigations to identify secondary causes of osteoporosis and review of x-rays of symptomatic areas.

All men with idiopathic osteoporosis and vertebral fractures were considered eligible for treatment. Exclusion criteria were a history of urinary tract stone disease, chronic renal impairment or allergy to bisphosphonates.

Baseline assessment
A clinical history was taken and examination performed. Investigations included urea, electrolytes, glucose, liver and thyroid function tests, full blood count and erythrocyte sedimentation rate, testosterone, sex hormone binding globulin, gonadotrophins, serum and urine protein electrophoresis and prostate-specific antigen. A urine sample collected after a 15-h fast was taken for measurement of calcium, creatinine, phosphate and hydroxyproline. X-rays of the spine and other symptomatic sites were performed at the bone clinic or, if available, obtained from the referring physician.

BMD measurement
BMD of spine (L1-L4) and hip (total hip, femoral neck, intertrochanteric and Ward's triangle) were measured at baseline and every 6-12 months. Results were expressed as areal density. Quality assurance measurements using phantoms supplied by the manufacturer were performed daily and it was deduced from these measurements that the performance of the densitometers was within accepted limits. During December 1992 the bone mineral measurement service upgraded its densitometer from a Hologic QDR-1000 to a Hologic QDR-2000 (Hologic Inc., Waltham, MA, USA). Although results from the two scanners were closely correlated, a comparative study with healthy volunteers showed a small systematic difference between measured BMD values and a correction for this has been applied (see Appendix). Precision for in vivo measurements was 1.0% at the lumbar spine and 1.5% for the total hip.

Treatment
Patients received oral intermittent cyclical etidronate therapy as disodium etidronate 400 mg daily on days 1-14, followed by 500 mg calcium as effervescent calcium citrate on days 15-90, after which the cycle was repeated continuously. All patients were instructed to take the etidronate on an empty stomach and the calcium supplements with or after food and their understanding of their treatment was reviewed periodically.

Follow-up
Patients were reviewed every 6 months, with enquiry for symptoms, BMD measurement, measurement of urea, electrolytes and bone chemistry of serum and fasting urine.

Statistical analysis
A regression line of BMD measurements over time was estimated for each patient and the rate of change of BMD estimated using the slope of this line. The hypothesis is that these slopes will have a negative mean, as a consequence of the normal age-related decline in BMD, if ICDT is ineffective. The precision of the slopes varied between patients as they were
Effect of ICDT on bone mineral density

estimated on between three and eight BMD measurements, so the estimate of average rate of change of BMD was weighted using the random-effects weights described by Matthews [19]. The standard error of the estimate was calculated and a 95% confidence interval for the true rate of change derived.

**Results**

To date, 42 men have completed more than 18 months of treatment, of whom 35 have completed 24 months of treatment. Median follow-up for the group as a whole is 31 months (range 18–45).

**Withdrawals and complications**

No patient discontinued etidronate therapy. Six patients who reported flatulence and/or dyspepsia with calcium citrate were transferred to chewable calcium carbonate 1.26 g daily (500 mg calcium).

**BMD measurement**

BMD increased at the lumbar spine in 40 of the 42 patients. One patient was excluded from the analysis as he had only two sets of evaluable results. Changes in mean BMD are shown for 15 randomly chosen patients in Figure 1. The average change was an increase of

![Graphs showing BMD results for 15 patients](image-url)
0.024 g/cm² per year of follow-up (95% confidence interval 0.017 to 0.032 g/cm²/year), which is equivalent to 3.2% of baseline values. BMD at the neck of femur increased in 23 of the 40 patients with sufficient data and decreased in the rest. The average change was an increase of 0.0078 g/cm²/year (95% confidence interval 0.0017 to 0.0139 g/cm²/year), which is equivalent to an average annual increase of 0.7% of baseline values.

There was no significant association between age and BMD change, as shown in Figures 2 and 3. Older

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**Figure 2.** Scatterplot of change in lumbar spine bone mineral density (BMD) against age at first scan. The regression coefficient (b) is expressed as change in BMD (g/cm²) per year of treatment. The fitted regression line has a coefficient of +0.00041 g/cm²/year (SE 0.00033) per year of age at recruitment; F = 1.61, P = 0.211.

**Figure 3.** Scatterplot of change in femoral neck bone mineral density (BMD) against age at first scan. The regression coefficient (b) is expressed as change in BMD (g/cm²) per year of treatment. The fitted regression line has a coefficient of −0.00045 g/cm²/year (SE 0.00026) per year of age at recruitment; F = 2.93, P = 0.095.
patients tended to have a slightly larger rise in lumbar spine BMD with treatment than younger patients ($P = 0.21$) but there was a trend towards loss of bone density at the hip in the older patients, whereas younger patients tended to have an increase in BMD at this site ($P = 0.10$). There was no association between change in BMD at the two sites—in particular, there was no evidence that gain in lumbar spine BMD was being attained at the expense of femoral neck BMD.

**Bone biochemistry**

The results of biochemical monitoring are shown in Table 1. Serum calcium and phosphate remained within reference ranges, while urinary calcium/creatinine and hydroxyproline/creatinine ratios did not differ significantly from baseline values at any time-point. Alkaline phosphatase fell in 26 of the 36 patients for whom this information was recorded. The average change in alkaline phosphatase was $-5.5\%$ of the baseline value (range $-43\%$ to $+57\%$). This fall was sustained in six patients but on average the alkaline phosphatase had returned to baseline values by 24 months.

**Discussion**

Our study shows that cyclical etidronate therapy in men with vertebral crush fractures is associated with a rise in bone density at the lumbar spine which is sustained over a 2-year period. An increase in lumbar spine BMD of 0.048 g/cm$^2$ over 2 years (95% confidence interval 0.034–0.064 g/cm$^2$) is equivalent to approximately 0.3–0.6 standard deviation units. As the risk of vertebral fracture has been observed to increase by a factor of about 2 ($range 1.4 - 2.8$) for each standard deviation unit decrease in BMD [20, 21], this increase in bone density should lead to a reduction in fracture risk of about 30% provided that the new bone is of normal quality. The change in BMD observed is thus both statistically significant and clinically meaningful. The trend towards bone loss at the neck of femur in older patients is a potential source of concern, but this association is weak and unlikely to be of clinical significance. Exclusion of the two outliers seen in Figure 3 results in the virtual disappearance of the association ($P > 0.3$).

Monitoring of bone chemistry was not particularly informative. Given the known anti-resorptive effect of bisphosphonates it should be possible to demonstrate a fall in markers of bone resorption on treatment, but we found no change in urinary calcium or hydroxyproline excretion. However these markers, which were widely used at the outset of this study, have now been superseded by more sensitive and specific assays such as urinary deoxypyridinoline and N-telopeptide.
This study cannot give a definitive answer as to the suitability of cyclical etidronate therapy for vertebral osteoporosis in men; to do so will require a randomized, placebo-controlled trial. Nonetheless, given the paucity of original data regarding the treatment of these patients, we feel that this observational study will contribute to the decision-making process for physicians dealing with men with idiopathic osteoporosis.

Our patients were a selected group only in that secondary osteoporosis was excluded and they varied widely in age, social background and educational attainment. Most patients found the treatment acceptable and most reported a perceived benefit of therapy. ICDT in the preparation licensed in the UK for use in postmenopausal women costs about £160 per annum and requires little in the way of clinical monitoring; this compares favourably with the high drug cost of some other preparations. Of the other treatments which might be of benefit, androgens have been shown to increase BMD [22] and are generally inexpensive, but the additional costs in staff time and investigations required to monitor therapy are appreciable. Fluoride preparations have a narrow therapeutic window, but there is now evidence for the efficacy and additional costs in staff time and investigations required to monitor therapy are appreciable.

Calcitonin is little used in the UK and is expensive.

In summary, therefore, intermittent cyclical etidronate therapy in men with osteoporosis has been shown in our study to be a feasible, well-tolerated therapy which produces a significant increase in BMD over a 2-year period. We conclude that this treatment is suitable for further evaluation in a randomized controlled trial.

Key points
- Osteoporotic vertebral fractures in men are common and cause substantial morbidity. There is no established treatment for idiopathic male osteoporosis.
- In this study, intermittent cyclical etidronate therapy significantly increased spinal BMD but there was no significant change in femoral neck BMD.
- Older patients responded as well as younger patients, with slightly greater increases in spinal BMD offset by a trend towards minor BMD loss at the femoral neck.
- Confirmation of the efficacy of this treatment requires a randomized controlled trial.

Acknowledgements

FA. was supported by an Action Research training fellowship.

References

Appendix. Bone mineral density measurement and quality assurance procedures

During the course of this study the bone mineral measurement service upgraded its densitometer from a Hologic QDR-1000 to a Hologic QDR-2000 (Hologic Inc., Waltham, MA, USA). As separate quality assurance (QA) phantoms were supplied with the two machines there was a difference in the QA results associated with the change in phantoms as well as the change in densitometers; consequently, QA results could not be compared directly. An ethically approved volunteer study was performed at the time of the densitometer upgrade to determine its effect on clinical results. Twenty-four volunteers were scanned on the QDR-1000 and then the QDR-2000 (in array mode). Measured lumbar spine BMD increased by 0.85% when compared with QDR-1000 results. Measured neck of femur BMD increased by 2.2% when compared with QDR-1000 results.

Because recruitment to the present study spanned the scanner changeover, almost all patients had baseline scans on the QDR-1000, with some or all subsequent scans on the QDR-2000; there was therefore an artefactual increase in measured lumbar spine BMD estimated at 0.85% and in femoral neck BMD of 2.2% in all scans after the changeover. A small number were scanned exclusively on the QDR-2000. Statistical analysis of the results of BMD measurement in the present study were performed using two data sets. Set A consisted of the actual results obtained from all patients with no corrections. Set B also included all patients, with the results of scans taken after the scanner changeover being multiplied by 0.9915 (lumbar spine) and 0.978 (femoral neck), i.e. corrected to the value which would have been obtained had the QDR-1000 been used throughout. Separate analyses showed only trivial differences in calculated coefficients (Table 1) and the interpretation of the results and thus the conclusions of the study, were unaffected by which dataset was considered. Corrected data (set B) have been used for all analyses in this paper.

Table 1. Comparison of regression slopes for corrected and uncorrected data

<table>
<thead>
<tr>
<th>Region</th>
<th>Data set</th>
<th>Slope (g/cm²/year)</th>
<th>Standard error</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td>A</td>
<td>0.0247</td>
<td>0.0033</td>
<td>0.0182, 0.0312</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.0240</td>
<td>0.0034</td>
<td>0.017, 0.032</td>
</tr>
<tr>
<td>Neck of femur</td>
<td>A</td>
<td>0.0030</td>
<td>0.0031</td>
<td>−0.0030, 0.0090</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.0078</td>
<td>0.0031</td>
<td>0.0017, 0.0139</td>
</tr>
</tbody>
</table>

95% CI, 95% confidence interval.
John Shaw, age 82.
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