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Timing of cyclical etidronate

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ABSTRACT

Objective

The importance of the timing of the etidronate component of cyclical etidronate was investigated in a study examining changes in lumbar spine BMD.

Methods

Seventy patients who had been taking cyclical etidronate for at least 1 year and who had baseline BMD studies and a further scan 1 year later were mailed a questionnaire asking about the time of day they took the etidronate component. Replies were received from 52 patients who were of average age 67.5 years (SD 6) and had been on therapy for an average of 2.7 years. Patients were divided into 3 groups according to when they took etidronate: Goup A - Fasting on waking, Group B - During the day, and Group C - Before retiring to bed or during the night. All patients except 2 claimed to avoid food and drink apart from water for 2 hours either side of taking etidronate.

Results

The mean increases in BMD over 1 year were 3.1% group A, -0.14% Group B, and 5.4% Group C and the total change over duration of use were 5.6%, 1.2% and 7.5%, respectively. There were significant differences ($P < 0.05$) between group B and the other 2 groups at 1 year and over 2.7 years.

Conclusion

We conclude that the 2-hour rule may be insufficient for taking etidronate during the day and that the etidronate component of cyclical etidronate is best taken in the early morning or late evening/at night.

Introduction

Following studies reported in the *New England Journal of Medicine* in 1990 by Storm *et al.* and Watts *et al.* (1, 2) oral etidronate has been widely used in the treatment of osteoporosis. Despite the lack of clear fracture efficacy in the above studies, cyclical etidronate has continued to be widely prescribed and at present constitutes around 40% of prescriptions for osteoporosis in the U.K. Further studies to the above have confirmed the benefits of cyclical etidronate in the improvement of BMD in osteoporosis with presumed, although not demonstrated, benefits in antifracture efficacy (3, 4). Therapy with this agent in clinical practice has largely followed the approach of the clinical trials with etidronate being given in a cyclical manner for 14 days at a dose of 400 mg/day as part of a 90-day cycle. Calcium supplementation has been given at a dose of 500 mg/day for the remaining 76 days. A proprietary pack (Didronel PMO) containing 400 mg etidronate for 14 days and 500 mg cacit for 76 days has been available from Proctor and Gamble Pharmaceuticals and is widely used in the U.K.

Post hoc analysis of data from the Fracture Intervention Trial of alendronate suggests that there is a greater antifracture efficacy in patients who have a greater rise in bone mass following treatment (5). Similar data does not exist for etidronate but variable bone density responses in different studies have been noted. For instance, in the U.S. multicentre study (2) where etidronate was administered 1-2 hours before breakfast, the average rise in spine BMD over 2 years was 4.2% and 5.2% in the treated groups. However, it is intriguing that in a study of Miller *et al.* much larger increases in spinal BMD were observed with etidronate given before bedtime (6). There was an average increase of 13% in the first year of therapy. If a greater rise in BMD following cyclical etidronate results in greater fracture efficacy, then the reason for different increases in BMD between studies deserves attention.

It is widely recognised that bisphosphonates are poorly absorbed via the gastrointestinal tract, and when prescribed orally it is advised that they be consumed on an empty stomach and for cyclical etidronate at least 2 hours either side of meals or drinks apart from water. The data of Miller *et al.* raises the possibility that this advice may be insufficient and the time of day of taking etidronate may be more important than generally recognised. This issue has not been formally assessed and this present study was performed to investigate the importance of the timing of the etidronate component of cyclical etidronate (Didronel PMO) on the change in lumbar spine BMD in patients on therapy as part of their clinical management.

Patients and methods

Bone density scan requests on patients referred to the osteoporosis unit who had had a previous bone density scan were prospectively examined over a 2-year period. Patients were referred for assessment of their fracture risk, detection of osteoporosis or to monitor their condition or its response to therapy. Questionnaires which asked about the nature of their therapy for osteoporosis and the length of treatment were routinely completed by all follow-up patients at the time of attendance for their scans. From the questionnaires all patients who attended for follow-up studies were noted if they were: 1) Taking cyclical etidronate as their only therapy; and 2) Had a baseline scan before therapy and at least 1 scan a year later. Seventy individuals were identified who fitted the above categories, and to them a questionnaire was then sent to enquire about when they took the etidronate component of cyclical etidronate, and how long they had been on therapy. In those who replied, the lumbar spine BMD (L1-L4) and femoral neck BMD were noted at baseline, 1 year and on any subsequent studies. All bone density scans were acquired on a Lunar DPX alpha, which remained stable over the course of the study.

The daily QC mechanism and daily phantom measurements over the period of study established this. The *in vitro* precision of the instrument was assessed from the daily aluminium phantom record and was calculated at 0.5% (7), which compares favourably with other systems (8, 9). The advice on cyclical etidronate was given by one physician familiar with the recommended approach to taking the treatment as advocated by the manufacturers of didronel PMO. Patients had not been previously on osteoporosis medications, and there was no reported intolerance.

Patients who responded were divided into 3 groups: (A) those who took etidronate fasting on waking, (B) those who took etidronate during the day, and those (C) who took etidronate before retiring to bed or during the night. The BMD changes at the lumbar spine and femoral neck were examined by comparing the baseline results to the measurements at 1 year and on any subsequent scans.

Results

Replies were received from 52/70 patients. They were 49 females and 3 males, and of average age 67.5 years (SD 6.0). They had been on treatment for an average of 2.7 (range 1- 5) years. The average interval between the baseline scan and the most recent scan was 2.2 years (range 1 - 4.5). The results are set out below with numbers in the 3 groups approximately equally divided (Table I). All patients appeared to have selected the time of day they took etidronate and continued with the same routine.

The baseline lumbar spine BMD and percentage change following treatment were examined, with the results set out in Table II. The results for femoral neck changes are shown in Table III. Results were analysed by the Student's t-test. There were significantly greater increases in lumbar spine BMD in the groups who took etidronate in the morning or evening compared to those who took it during the day ($p < 0.05$). There was no significant difference between those who took etidronate in the morning or evening.

Four patients were known to have vertebral fractures at baseline (Genant grade 2 or 3) affecting one or more of the upper first four lumbar vertebrae and all took etidronate in the evening/night. Exclusion of these patients increased the mean baseline spine BMD to 0.841 g/cm^2 and reduced the percentage change in spine BMD in the evening group at 1 year to +4.1% and overall to +6.1%, but did not affect the significance of the results. Four patients did not follow the 2-hour rule, among whom 3 took etidronate upon waking and then had food less than 2 hours afterwards. All of these patients had rises in spine BMD and exclusion of them did not alter the results. One patient took etidronate during the day and consumed food less than 2 hours after etidronate, but again exclusion of this patient did not affect the result. The femoral neck BMD changes did not show any significant differences between the 3 groups ($p > 0.05$).

Discussion

The lumbar spine bone density results from this study show a significant difference in the change in spine BMD according to the time of day when patients

Table I. Patient characteristics.

Timing of Etidronate	Numbers	Age (mean yrs.)	Mean years of treatment	Mean years between initial and latest scan
Morning	13	68	2.8	2.6
Day	19	67	2.6	2.2
Evening	20	68	2.6	1.9
Total	52	68	2.7	2.2

Table II. Percentage change of lumbar spine BMD following treatment.

Timing of etidronate	Mean baseline BMD	Mean (SD)% first year change of BMD	Mean (SD)% total change of BMD
Morning	0.887 g/cm^2	+3.1 (3.1)	+5.6 (3.2)
Day	0.828 g/cm^2	-0.14 (5.6)	+1.2 (5.7)
Evening	0.827 g/cm^2	+5.6 (7.4)	+7.5 (7.4)

Table III. Percentage change of femoral neck BMD following treatment.

Timing of etidronate	Mean baseline BMD	Mean (SD)% first year change of BMD	Mean (SD)% total change of BMD
Morning	0.734 g/cm^2	+2.5 (5.2)	+1.0 (6.1)
Day	0.692 g/cm^2	+0.77 (5.4)	+2.0 (5.5)
Evening	0.737 g/cm^2	+1.3 (4.3)	0 (4.9)

consumed the etidronate component of cyclical etidronate. Patients had a greater rise in bone mass when etidronate was taken during the evening or at night as opposed to the day, even though all patients appeared to carefully follow instructions to avoid food and beverages apart from water for 2 hours before or after the medication. This work lends support to observations from the study of Miller *et al.* (6), where there was an average rise in lumbar spine BMD of 15.7% over 2 years with patients advised to take etidronate at bedtime, suggesting that the time of day of consumption of etidronate may be important. In that study there were 47 patients on cyclical etidronate of average age 64 years and with a baseline BMD of 0.894 g/cm^2 with measurements made on a Lunar DP3 dual photon absorptiometer. The age and BMD of the patients were therefore not dissimilar to those for the patients in the present study.

It should be noted that all the patients in the above study of Miller *et al.* had one or more baseline vertebral fractures and these could be either thoracic or lumbar fractures. The study authors do not comment on the number of lumbar spine fractures. They do state that there were no new fractures in any of the treated patients during the study, using as their criteria for a new fracture a > 25% reduction in the anterior or posterior vertebral height. No comment was made on the progression of pre-existing fractures. There is therefore a possibility that the large rises in bone mass in that study could have been related to relatively minor new vertebral deformations or to a progression of existing lumbar fractures, as either of these would tend to increase bone mass (10). The authors of this paper also suggest that their patient population may have had higher bone turnover than in other reported studies or may have been stricter in following advice on taking etidronate with respect to food and beverages, but offer no supporting data.

We had relatively few individuals with pre-existing fractures and the patients, as far as we could establish, were careful to follow the 2-hour rule with respect to etidronate. Experience in clinical practice suggests that most patients are conscientious in following the 2-hour rule, supporting the likelihood that etidronate was taken in the correct manner. The rises in BMD were more comparable to other reported studies of cyclical etidronate (1-3), suggesting that although the time of day of the consumption of etidronate is important, it is not the only explanation for the large BMD increases found in the work of Miller *et al.* The paper of Miller *et al*. does not state the length of time after the previous consumption of food and beverages that lapsed before didronel could be consumed. If advice and patient practice was significantly greater than 2 hours it is still possible that bioavailability is at least the cause of the large increases in BMD. Unlike this study, in the Miller study phosphorus was given for 3 days before etidronate according to the ADFR concept. However, phosphorus was given in the multicentre U.S. trial of Watts *et al.* and the rise in spinal BMD observed was similar to ours (2).

The difference in the BMD increases in this present study between the 3 groups is presumed to be related to the poorer bioavailability during the day when there may be food or substances found in beverages still in the stomach or intestine interfering with absorption. Those taking etidronate first thing in the morning or at night would have had a much longer time interval between the consumption of didronel and the consumption of substances that might interfere with absorption. For patients taking etidronate before retiring to bed it is likely that there would also be a longer interval between taking etidronate and food and beverages. The importance of the different time intervals between didronel and possible interfering food items is likely to be relevant, as calcium-containing foods may affect etidronate absorption for up to 6 hours after consumption (11, 12). It has to be accepted that alternative explanations for the differences between the study groups may exist and these could include variable compliance, rates of bone turnover (13) or genetic factors (14). Other influences such as differences in activity, calcium intake, confounding medication or medical conditions and weight change may also be important. No assessment could be made of the progression of degenerative change or the development of new fractures. Patients who failed to respond to the questionnaire may also have biased the results.

The lack of a significant difference in BMD changes at the femoral neck between the 3 groups could relate to smaller increases in BMD at this site, with etidronate requiring much larger numbers of patients to show a significant effect. It should be noted that there was a trend to a lower increase in BMD in group B at the femoral neck at 1 year. However, the lumbar spine is perhaps the more important site to consider because it is the usual site for assessing response to therapy because of the larger changes in BMD with bisphosphonates, compared to the hip.

The data from this present study suggests that patients who are prescribed cyclical etidronate should take their medication at night or in the early morning before breakfast. If taken during the day, the 2-hour recommended interval between etidronate and other food products is insufficient. A minority of patients admitted to not following the 2-hour rule for consuming food or beverages before or after etidronate, suggesting that the advice given on the initial prescription of etidronate requires reinforcement at later intervals.

This data is from a retrospective analysis and it is recognised that other confounding variables may have biased the results. A more rigorous prospective study is advocated following these observations. There may of course be implications from the results of this study regarding other bisphosphonates, and this aspect of bisphosphonate therapy deserves further evaluation.

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