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USE OF CYCLICAL ETIDRONATE AND PREVENTION OF NON-VERTEBRAL FRACTURES

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SUMMARY

This study examined the effects of cyclical etidronate, when used in routine clinical practice, on the prevention of fracture. Information was obtained from 550 general practices in the UK that provide their medical records to the General Practice Research Database. A total of 7977 patients taking cyclical etidronate treatment and 7977 age-, sex- and practice-matched control patients with a diagnosis of osteoporosis were analysed. People taking cyclical etidronate had a significantly reduced risk of non-vertebral fracture (by 20%) and of hip fracture (by 34%) relative to the osteoporosis control patients. The relative risk of non-vertebral fracture was 0.80 (95% confidence interval 0.70–0.92), that of hip fracture 0.66 (0.51–0.85) and that of wrist fracture 0.81 (0.58–1.14). When fracture incidence rates were compared between the two groups, the rate of non-vertebral, hip and wrist fracture decreased significantly ($P < 0.05$) with increasing etidronate exposure. The results of this study complement and extend clinical observations supporting the anti-fracture efficacy of cyclical etidronate therapy.

KEY WORDS: Cyclical etidronate, Osteoporosis, Fractures, Epidemiology.

OSTEOPOROSIS is a common skeletal disorder, characterized by decreased bone mass and disrupted bone architecture, that results in reduced bone strength and an increased risk of fracture [1–3]. The major clinical manifestations include vertebral, wrist and hip fractures, and these constitute a major health problem among the elderly [4]. Many drugs are capable of decreasing the rate of bone loss in osteoporosis. However, the degree to which bone loss is retarded may not always predict the extent of fracture prevention [5–7]. It is, therefore, necessary to study the direct effects of drug intervention on fracture risk [8].

Most clinical trials using fracture as an end point have been confined to vertebral fracture; however, most of the morbidity and mortality associated with osteoporosis results from non-vertebral fractures. The correlations between bone mineral density measured at different skeletal sites are modest and risk factors vary between different fracture sites [9, 10]. Also, there may be difficulties in generalizing from clinical trial patients to patient populations in routine clinical practice due to selective patient participation and differences in treatment compliance and patient monitoring [11–13]. Observational research can complement and extend the findings of randomized controlled trials [14–17]. The major limitations of observational research are that control for confounding (i.e. baseline differences) may be incomplete and that patients and prescribers are not blinded to treatment.

The purpose of this report is to document, in a general practice setting, the fracture rates among persons receiving cyclical etidronate compared to persons with a diagnosis of osteoporosis who were not taking a bisphosphonate.

SUBJECTS AND METHODS

General practitioners (GPs) play a key role in the health care system in the UK as they are responsible for primary health care and specialist referrals. The information in this study was obtained from the General Practice Research Database (GPRD), which contains the computerized medical records of 550 general practices including 3.5 million people. The data recorded in the GPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes [18–22]. Clinical data are stored and retrieved by means of OXMIS codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9) [19, 22]. Each entry into the GPRD is internally validated by cross-checking within the practice and by comparisons with external statistics [18–22]. Only data from practices that pass this quality control are compiled to form the GPRD. Several independent validation studies have confirmed a high level of completeness and validity of the GPRD [23–26]. In the largest validation study, the sensitivity and positive predictive value of most conditions reviewed (including non-vertebral fractures) were found to be $>90\%$ [26].

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Study population

The etidronate takers in this study were patients who received one or more cyclical etidronate prescriptions (14 days of etidronate followed by 76 days of calcium). The indication for cyclical etidronate in the UK was treatment of established vertebral osteoporosis. The control patients were patients with osteoporosis recorded in their medical record, but no bisphosphonate use; they were matched by age (within 5 yr and, if no patient found, within 10 yr), gender and, if possible, medical practice. The baseline date for each control patient was defined as the baseline date of their matched etidronate taker (i.e. first etidronate prescription). For a small number of control patients who had transferred to another practice or died prior to baseline, a baseline date was selected randomly between the registration and transfer dates. Each etidronate taker was followed from baseline until they sustained a fracture, until 6 months after the last etidronate prescription, or until the patient's change of practice, death or end of the study in July 1995 (whichever date came first). Control patients were followed until fracture, or end of follow-up of their matched etidronate taker, the patient's change of practice, death or end of study. The objective of this design was to have comparability of age and gender between the different groups, and to have the information collected from within the same practice and over a similar time period. A non-osteoporosis control patient (i.e. without osteoporosis recorded and matched by age, gender and practice) was also selected randomly and used to evaluate the validity of fracture information and the composition of our study cohorts with respect to the severity of osteoporosis.

Fractures were sought in the medical records of each subject during follow-up. The fractures, based on ICD-9 categories, included non-vertebral and vertebral fractures. Factors associated with the development of osteoporosis, the likelihood of falling or the treatment of osteoporosis were identified within the database and considered as potential confounding variables [27–46]; these included diabetes mellitus, rheumatoid arthritis, hyperthyroidism, congestive heart failure, seizures, anaemia, dementia, depression, cerebrovascular accident, falls, and a history of fractures and back pain prior to baseline. Prescriptions during follow-up for anticonvulsants, methotrexate, corticosteroids, thiazide diuretics, anxiolytics, anti-psychotics, anti-depressants, anti-Parkinson drugs, hormone replacement therapy, vitamin D and calcitonin were also considered potential confounding variables [27–46]. Baseline risk factor information was ascertained using the entire medical record of a patient, irrespective of the length of time between the practice enrolment date or patient's registration date and the baseline date of the patient.

Statistical methods

Incidence rates of hip, wrist, vertebral and all non-vertebral fractures were estimated by dividing the number of patients with a fracture by the total number of patient-years of follow-up. This method for estimating incidence is widely used in circumstances characterized by varying durations of follow-up [47, 48]. The principal outcome measure in this study was the number of patients with a fracture, rather than the number of fractures. The reason for this was that multiple fractures in the same patient may not be independent events [49]. Adjusted relative rates were estimated using a Poisson regression model that included selected confounding variables. Confounding variables that either caused a change in the crude rate of at least 10% or were strongly associated with the development of a fracture (unadjusted relative risk of >1.50 or <0.67 in our data set) were included in the regression model on the basis of the goodness of fit [50]. Confidence intervals were based on the method for test-based intervals [47]. Cumulative survival curves were also constructed and Cox proportional hazards models fitted.

Incidence rates were estimated for the first year of treatment/follow-up, second year, and third year or later. The presence of a linear trend over these years was estimated for each cohort separately using Poisson regression. This analysis concerned the incidence patterns in the etidronate cohort irrespective of the control group. The linear trends were also compared between the two groups. The linear trend difference (i.e. angle between the two trends) was estimated using a Poisson regression model that included confounding variables and, if significant, the baseline fracture history.

RESULTS

The etidronate cohort, including 7977 patients of whom 7244 were women, was followed for a mean period of 1.29 yr per person. A total of 1829 patients were treated for 2 yr or more. All the cyclical etidronate takers were matched for gender and age within 10 yr; ~80% of the cyclical etidronate takers were matched within practice to an osteoporosis control. The two cohorts had follow-up information collected at comparable calendar time.

The etidronate and control cohorts were comparable with respect to age and gender (Table I). Cyclical etidronate takers were more likely to have a history of back pain in the previous year (39.9% of etidronate takers *vs* 13.1% among controls), of vertebral fractures (8.8% *vs* 1.1%) and of use of corticosteroids (26.0% *vs* 14.0%). The two cohorts were more comparable with respect to history of non-vertebral fractures (6.8 and 4.5%, respectively) and history of falls (5.3 and 5.4%, respectively).

Table II shows the non-vertebral fracture incidence by comparison group. In the etidronate group, the incidence of non-vertebral fractures was 3.9/100 patient-years compared to an incidence of 4.7 in the control group. Adjustment for confounding variables did not change the relative risk of non-vertebral

TABLE I
Characteristics of etidronate and osteoporosis control group

	Cyclical etidronate group (N = 7977)	Osteoporosis control group (N = 7977)
Total duration of follow-up (patient-years)	10.328	9342
Mean	1.29	1.17
Median	0.99	0.86
Women	7244 (90.8%)	7244 (90.8%)
Age (yr)		
Mean	71.6	73.4
Median	73	74
Disease history in year prior to baseline*		
Back pain	2514 (39.9%)	808 (13.1%)
Falls	334 (5.3%)	332 (5.4%)
Osteoporosis/vertebral osteoporosis	4603 (73.1%)	1062 (17.2%)
Prescription history in year prior to baseline*		
Corticosteroids (oral, suppository, parenteral)	1635 (26.0%)	864 (14.0%)
Calcium	1539 (24.4%)	1513 (24.5%)
Hormone replacement therapy	525 (8.3%)	758 (12.3%)
Fracture history in year prior to baseline*		
Non-vertebral fracture	431 (6.8%)	277 (4.5%)
Vertebral fracture	556 (8.8%)	65 (1.1%)
Vertebral X-ray in year prior to baseline*	881 (14.0%)	181 (2.9%)
Hip/wrist X-ray in year prior to baseline*	174 (2.8%)	73 (1.2%)

*Information is derived from 78% of the cohort (12 470 people) with at least 1 yr retrospective information prior to baseline.

fractures (adjusted relative risk of 0.80). People taking cyclical etidronate had a significantly reduced risk of hip fracture (by 34%) relative to the osteoporosis controls [relative risk = 0.66; 95% confidence interval (CI) 0.51–0.85]. The greatest effect on hip fracture risk was seen in females aged 76 yr or older who experienced a risk reduction of 44% (relative risk = 0.56; 95% CI 0.41–0.77). Wrist fractures occurred less frequently in the etidronate group, although the difference was not statistically significant (relative risk = 0.81; 95% CI 0.58–1.14).

Within the etidronate cohort, the incidence of non-vertebral fractures decreased significantly over time (test for linear trend over yr 1–3+; P = 0.01). The incidence was 4.3% in the first year of treatment, 3.4% in the second, and 2.9% in the third year and later (Table II). In contrast, fracture incidence remained stable in the control group. When comparing the slope of fracture incidence over time between the two groups, the rate of decline was significantly greater in the etidronate cohort for non-vertebral, hip and wrist fractures compared to the control group. Figure 1 illustrates a survival plot of the proportion of subjects free of fracture over time according to treatment group.

The two groups were not comparable at baseline for vertebral fracture risk, with a higher baseline risk for the etidronate cohort (vertebral fracture history in 8.8% of etidronate takers and 1.1% of control patients). When comparing the overall incidence between the two groups, the vertebral fracture risk of cyclical etidronate takers was reduced to a level similar to that experienced by the less severely affected osteoporosis control patients (relative risk = 1.26; 95% CI 0.95–1.67). The difference between the crude and adjusted relative rate was substantial (1.60 *vs* 1.26, respectively), supporting the notion that the etidronate and control cohorts were not comparable in the distribution of confounding variables.

Within the etidronate cohort, the vertebral fracture risk decreases significantly over time (test for linear trend over yr 1–3+; P = 0.002). The incidence was 1.8% in the first year of treatment, 0.9% in the second, and 1.0% in the third year and later. In contrast, fracture incidence remained stable in the control group. When comparing the slopes of the

TABLE II
Incidence of non-vertebral fractures over time by comparison group

	Cyclical etidronate group			Osteoporosis control group		
	Exposure (patient-years)	Number of cases	Fracture rate (%)	Exposure (patient-years)	Number of cases	Fracture rate (%)
Baseline	6300*	431	6.8	6170*	277	4.5
Year 1	6020	256	4.3	5775	280	4.8
Year 2	2651	91	3.4	2259	97	4.3
Year 3+	1273	37	2.9	937	45	4.8
Total	9943	384	3.9	8970	422	4.7
Adjusted relative rate	0.80 (95% CI 0.70–0.92)					

*Information is derived from 78% of the cohort with at least 1 yr retrospective information prior to baseline.

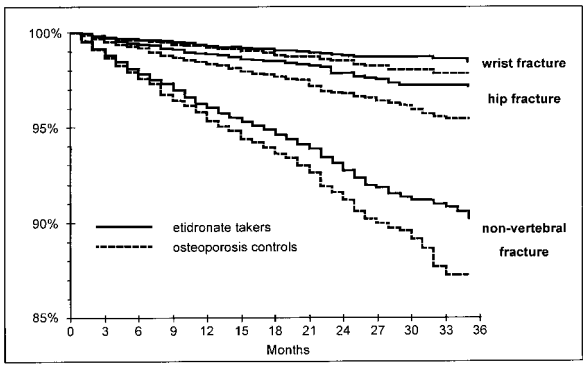

FIG. 1.—Cumulative proportion of people without non-vertebral, hip or wrist fracture by comparison group.

fracture rates over time between the two groups and taking into account their baseline fracture risk, vertebral fracture incidence decreased significantly in the etidronate cohort relative to the control group.

DISCUSSION

We found that patients who received cyclical etidronate treatment had a lower risk of non-vertebral fracture, including hip fractures, than the control patients with a diagnosis of osteoporosis. The results of our study are consistent with the results of randomized clinical studies on the effects of bisphosphonates. Progressive increases in bone mass at the spine and hip, as well as significant reductions in fracture rate, have been observed with cyclical etidronate and other bisphosphonates [51]. Both cyclical etidronate and alendronate have been found in clinical trials to reduce vertebral fracture incidence by ~50% [52–55]. In the largest clinical trial of a bisphosphonate to date, a 51% reduction in the risk of hip fracture was found with alendronate [55]. Although no comparative studies have been conducted and there are substantial differences between these studies in design, sample size and patient characteristics, the data suggest that different bisphosphonates may have comparable efficacy in post-menopausal osteoporosis [51]. A comparative randomized trial would be needed to test this notion fully. With respect to safety, alendronate has been associated with an increased incidence of oesophagitis [56]. In our study population, the incidence of upper gastrointestinal events, including oesophagitis, was found to be comparable between the cyclical etidronate and control groups [57].

There are several limitations of this observational study relative to a prospective randomized clinical trial. Control for confounding was restricted to age, sex and a variety of medical diagnoses and treatments. A number of potential confounders were not recorded systematically in the database (e.g. diet, obesity or physical activity). However, adjustments for known confounders had little effect on non-vertebral fracture rates, and the baseline characteristics of the etidronate population suggest that treatment was given for vertebral osteoporosis rather than for non-vertebral osteoporosis. Another limitation of the study was that neither prescriber nor patient were blinded to treatment. The prescriber may have been more alert to fractures in the treated group; however, this increased awareness is less likely to affect hip and wrist fracture ascertainment. Overdiagnosis of fractures in the treated group would, in fact, be expected to lead to a higher rate of fracture in the etidronate group, biasing the study against a positive finding and underestimating the effects of the drug. A well-designed prospective randomized clinical trial would eliminate this bias.

The data for our study were obtained from computerized medical records used by GPs in the UK for their daily patient management. Although the practices in this study were selected for computerization and high-quality data provision, the patient population included in the GPRD database is broadly representative of the UK population as a whole. These data have also been validated for use in epidemiological studies [18–26]. Etidronate takers were compared to a control group who had, as expected, a lower baseline risk for vertebral fractures, given that the indication for cyclical etidronate in the UK is established vertebral osteoporosis. Over the course of therapy, however, their vertebral fracture risk was reduced. Conversely, the baseline characteristics for non-vertebral fracture were similar between the comparison groups. The non-vertebral fracture risk was significantly reduced in the etidronate group and during the course of the follow-up period the etidronate group showed a significant trend towards lower non-vertebral fracture rates. The higher use of corticosteroid in the etidronate cohort is not unexpected as compression fractures of the spine are usually the first sign of glucocorticoid-induced bone loss [58].

Diagnostic information was obtained in this study from GPs who recorded either their own diagnosis or the information received from specialist care. Information on the method of diagnostic ascertainment of each fracture and about bone mass was not available. One possible explanation for the lower non-vertebral fracture rate in the etidronate group could be a differential likelihood of fracture diagnosis, with etidronate takers less likely to be diagnosed with a fracture at a given severity of symptoms. However, this explanation seems unlikely for a cohort of patients who were treated for the underlying disease and who were more likely to have undergone vertebral radiography. In most clinical studies, the presence of vertebral fractures is ascertained through radiographic measurements. The means whereby vertebral fracture or osteoporosis were diagnosed could not be ascertained in this study. However, the limited availability of bone densitometry to GPs in this country, and the relatively low rate of referral to specialist care, make it likely that the diagnoses of vertebral fracture were based on clinical and radiographic assessments. This notion is supported by the correlation of vertebral fracture with back pain, and the similarity between vertebral

fracture incidence in our study population and published rates for clinically diagnosed vertebral fractures [28, 59].

Several analyses were conducted to review the sensitivity of the results to the method of analysis. When excluding patients with a baseline fracture history, similar non-vertebral fracture reductions were seen in the etidronate cohort (relative risk = 0.76). This 'first-ever fracture' analysis further reduced the differences between the comparison groups for vertebral fractures (relative risk = 0.96), which is consistent with the notion that the two cohorts were not comparable with respect to baseline presence of vertebral deformities. The two groups were also compared for the incidence slopes over time of back pain (a major symptom of vertebral fracture) and of vertebral osteoporosis (a general description of vertebral deformities). It was found that the incidence in the etidronate cohort decreased significantly over time for these conditions compared to the control group. Our final analysis utilized Cox proportional hazards models which yielded results similar to the Poisson regression.

In order to evaluate the validity of fracture information and the composition of our study cohorts with respect to the severity of osteoporosis, we compared the fracture rates in the GPRD to population incidence data derived from the literature [28, 59–61]. Fracture incidence rates among females were estimated during the period of time from the GPRD enrolment date of the practice up to the end of data collection for the control patients or up to the first etidronate prescription for the later etidronate takers (i.e. this reflects the experience prior to etidronate exposure). The hip fracture incidence increased with age in all three GPRD cohorts,

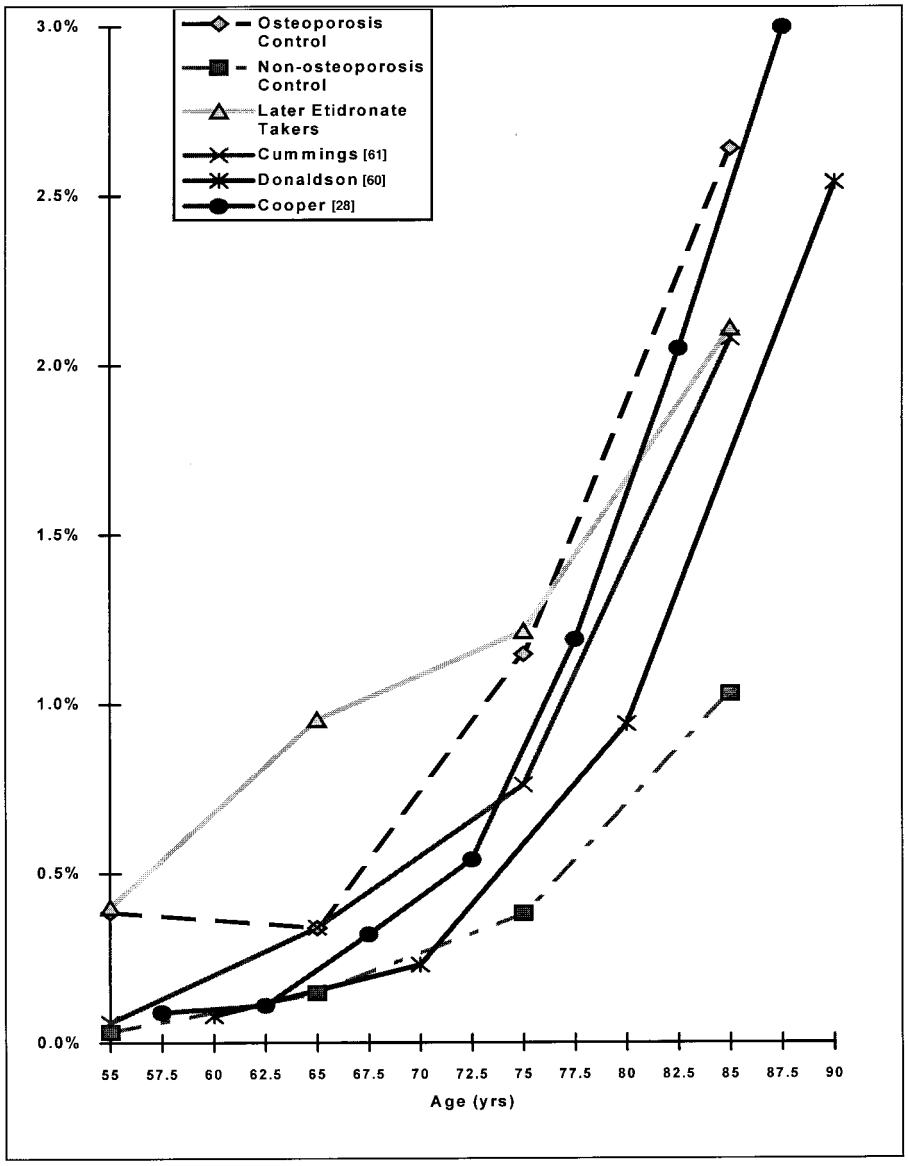

FIG. 2.—Incidence of hip fractures among women by age in this and other epidemiological studies.

consistent with published population-based data (Fig. 2) [28, 59–61]. Conversely, wrist fractures remained stable over age in the GPRD cohorts, as described in the literature for these age groups [28, 59–61]. The vertebral fracture incidence rates were similar between the GPRD osteoporosis control patients and published data for clinically diagnosed vertebral fractures [28, 59]. Within the GPRD, the later etidronate takers had the highest vertebral fracture rates (prior to etidronate exposure) with virtually no vertebral fractures occurring among the non-osteoporotics. The relative risk stratified by age was 5.24 for vertebral fractures in later etidronate takers compared to osteoporosis controls and 88.20 compared to non-osteoporosis controls. The non-vertebral relative risks were 1.31 and 2.72, respectively. The larger differences in vertebral fracture risks are consistent with the indication for treatment with etidronate. Smaller differences were found for non-vertebral fractures between later etidronate takers and osteoporosis controls. These data also support the notion that at baseline etidronate takers were more likely to have sustained previous fractures (especially vertebral fractures). As a prevalent fracture is a strong predictor of recurrent fracture, a bias towards higher fracture rates in the etidronate group would be expected.

The natural course of vertebral fractures is episodic. After each vertebral fracture, latent intervals of relatively little discomfort and disability follow [62, 63]. The finding of a vertebral fracture incidence of 8.8% at baseline *vs* 1.4% after the start of etidronate treatment may be explained (partly) by the episodic course of vertebral osteoporosis. However, the episodic occurrence of deformities does not explain the continued decrease in incidence over time observed in the etidronate cohort since the symptoms start to recur after the latent interval [63]. The non-vertebral fracture reductions are also not readily explained in this way. The analysis of baseline characteristics supports the notion that etidronate was prescribed for vertebral osteoporosis rather than for non-vertebral osteoporosis. Also, the decrease in incidence over time in the etidronate cohort is not consistent with an episodic course of non-vertebral fractures. An analysis excluding people with a fracture history yielded similar results for non-vertebral fractures.

We conclude that the results complement and extend clinical observations supporting the anti-fracture efficacy of cyclical etidronate therapy. The risk of non-vertebral fractures, including hip fractures, was significantly reduced with cyclical etidronate treatment; that of vertebral fractures was also reduced significantly over the treatment duration.

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