Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure

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Abstract

***Objective*—To determine whether alfacalcidol—used in management of overt renal bone disease—may safely prevent renal bone disease when used earlier in course of renal failure.**

***Design*—Double blind, prospective, randomised, placebo controlled study.**

***Setting*—17 nephrology centres from Belgium, France, the Netherlands, and the United Kingdom.**

***Subjects*—176 patients aged 18-81 with mild to moderate chronic renal failure (creatinine clearance 15-50 ml/min) and with no clinical, biochemical, or radiographic evidence of bone disease.**

***Interventions*—Alfacalcidol 0·25 μg (titrated according to serum calcium concentration) or placebo given for two years.**

***Main outcome measures*—Quantitative histology of bone to assess efficacy of treatment and renal function to assess safety.**

***Results*—132 patients had histological evidence of bone disease at start of study. Biochemical, radiographic, and histological indices of bone metabolism were similar for the 89 patients given alfacalcidol and the 87 controls given placebo. After treatment, mean serum alkaline phosphatase activity and intact parathyroid hormone concentration had increased by 13% and 126% respectively in controls but had not changed in patients given alfacalcidol ($P<0·001$). Hypercalcaemic episodes occurred in 10 patients given alfacalcidol (but responded to decreases in drug dose) and in three controls. Histological indices of bone turnover significantly improved in patients given alfacalcidol and significantly deteriorated in controls: among patients with abnormal bone histology before treatment, bone disease resolved in 23 (42%) of those given alfacalcidol compared with two (4%) of the controls ($P<0·001$). There was no difference in rate of progression of renal failure between the two groups.**

***Conclusion*—Early administration of alfacalcidol can safely and beneficially alter the natural course of renal bone disease in patients with mild to moderate renal failure.**

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BMJ 1995;310:358-63

Introduction

Renal bone disease is more or less universal in patients with end stage renal failure, and abnormalities in bone histology may be detected in a large proportion of patients with a creatinine clearance of < 60 ml/min.[1] Patients found to be at particular risk of developing renal bone disease are children, women, those with a long history of renal impairment, and those with predominant tubulointerstitial renal lesions.[2] The reported prevalence of renal osteodystrophy varies substantially between studies, however, largely due to differences in the diagnostic criteria used to identify bone disease.[3-5]

The pathogenesis of renal osteodystrophy is complex and multifactorial,[5,6] but absolute or relative deficiency of 1,25-dihydroxycholecalciferol (the active metabolite of vitamin D) has a causal role in its development.[7-10] As renal failure advances, the decrease in functional renal mass and hyperphosphataemia results in a decrease in the renal 1α-hydroxylase activity, thus decreasing production of 1,25-dihydroxycholecalciferol.[11-13] Deficiency of 1,25-dihydroxycholecalciferol decreases the intestinal absorption of calcium and so contributes to hypocalcaemia, which is the main stimulus for parathyroid hormone secretion and, more arguably, for parathyroid hyperplasia. Hypocalcaemia is not, however, the sole stimulus for parathyroid hormone secretion.[14] Deficiency of 1,25-dihydroxycholecalciferol also increases skeletal resistance to the effects of parathyroid hormone and increased parathyroid cell proliferation and secretion, all contributing to hyperparathyroidism.[15-19] Since adequate serum concentrations of 1,25-dihydroxycholecalciferol may be required for normal parathyroid function, there is a case for using this metabolite of vitamin D or related analogues early in the course of renal failure to prevent parathyroid hyperplasia and its skeletal consequences.

The 1α-hydroxylated derivatives of vitamin D have been widely and successfully used to manage renal bone disease in patients having dialysis since the early 1970s, but there is less experience with their use in early renal failure. The results of 20 open and controlled studies in early renal failure on a total of some 220 patients were recently reviewed.[20] Calcitriol (1,25-dihydroxycholecalciferol) had beneficial effects on renal bone disease, but the incidence of hypercalcaemia was high; serious reservations were raised about calcitriol's possible adverse effects on renal function, either because of a direct toxic effect on the kidney or because of an indirect effect as a result of hypercalcaemia. These concerns have limited the more widespread use of calcitriol and its analogues to alter the natural course of renal bone disease in patients with renal failure who do not yet require dialysis. We wished to determine whether moderate doses of alfacalcidol (1α-hydroxycholecalciferol) might safely be used in patients with early renal failure to prevent renal osteodystrophy.

Patients and methods

We studied 176 patients, 107 men and 69 women, aged 18-81 in a multicentre, prospective, randomised, double blind, placebo controlled study. The study was conducted in 17 centres in four countries—Belgium (23 patients), France (44 patients), the Netherlands (38 patients), and the United Kingdom (71 patients). Informed consent was obtained from all patients, and the study was approved by the relevant ethics committees of participating centres.

Patients were considered eligible for entry into the study if their rate of creatinine clearance was 15-50 ml/min and they had no clinical, biochemical, or radiographic evidence of renal bone disease. Exclusion criteria were symptomatic bone disease, a raised serum calcium concentration or total alkaline phosphatase activity, and a disturbance in liver function (as judged by a 1·5 fold increase or more in liver aminotransferase activity). The aetiology of renal disease was classified as glomerulovascular (glomerulonephritis, hypertension,

or diabetes—107 patients), tubulointerstitial (polycystic kidneys, analgesic nephropathy, reflux nephropathy, or kidney stones—55 patients), or unknown (14 patients).

TREATMENT

Patients were randomly allocated to receive alfacalcidol or placebo. The starting dose for alfacalcidol was 0·25 μg daily as a single morning dose, and doses were adjusted between 0·25 μg every other day to 1 μg a day in order to maintain serum calcium concentration at the upper limit of the normal laboratory reference range. Treatment was continued for two years or until the patient required dialysis.

None of the patients had previously received calciferol (vitamin D) or any of its metabolites before entry into the study, but calcium supplements, when previously taken, were continued up to a maximum daily dose of 500 mg of elemental calcium. The use of phosphate binding drugs other than calcium was permitted when dietary restriction of phosphate failed to maintain serum phosphate concentrations below 2·2 mmol/l, and the doses given were documented. All other drugs required for the daily management of patients were also allowed and the doses documented.

BIOCHEMICAL ASSESSMENT

Biochemical assessments were undertaken at the start of the study and at regular intervals thereafter. Serum concentrations of creatinine, calcium, and phosphate and activities of alkaline phosphatase and liver enzymes were measured every month for the first six months, every three months for the next six months, and then every six months. Measurements were made with a standard SMAC analyser, and patients were recalled earlier if they were found to be hypercalcaemic or for other clinical reasons. Serum calcium concentrations were adjusted for fluctuations in albumin concentration. Mild hypercalcaemia was diagnosed when serum calcium concentration was above the upper limit of the laboratory reference range (>2·63 mmol/l) on at least two consecutive occasions, and severe hypercalcaemia was diagnosed when serum calcium concentration was greater than 3·00 mmol/l on any one occasion.

Twenty four hour urine samples were collected at the same time as blood samples, and creatinine concentration was measured with standard procedures. The glomerular filtration rate was estimated every six months, both as the endogenous creatinine clearance alone and after adjustment for body surface area.[21] Concentrations of calcium, phosphate, and hydroxyproline were also measured in the same 24 hour urine samples in the British centre.

Samples for assay of parathyroid hormone activity were collected at six month intervals, stored at −20°C, and assayed blind in one centre at the end of the study with a chemiluminescent assay for intact human parathyroid hormone (MagicLite, Ciba Corning). The detection limit of the assay is 0·4 pmol/l, and the reference range in normal subjects is 0·8-5·4 pmol/l.[22] The coefficient of variation is less than 10% for parathyroid hormone concentrations greater than 1 pmol/l. Sequential samples for individual patients were assayed in one batch. Assays for serum alkaline phosphatase activity were repeated in a central laboratory at the end of the study (reference range 110-300 IU/l). Blood samples for estimating serum aluminium concentration were collected from about 60% of patients.

RADIOGRAPHS

Radiological assessment was undertaken with plain posterioanterior radiographs of the hands at the start of the study, after one year, and at the end of the study and were evaluated blind at the end of the study.

BONE HISTOLOGY

All patients underwent a tetracycline double labelled transiliac bone biopsy at the start and, when possible, the end of the study. A second bone biopsy sample from the opposite ilium was obtained in 134 patients (76%). The biopsy was undertaken under local anaesthesia with a modified Meunier bone biopsy trephine with a 4-8 mm internal diameter. Bone samples were processed for light and ultraviolet light microscopy.[24] The presence of aluminium at the mineral-osteoid interface was assessed with aurintricarboxylic stain (Aluminon).[25]

Qualitative, semiquantitative, and quantitative analyses of bone biopsies were undertaken blind by one observer (MNCB) at the end of the study. Qualitative assessments were made for the presence or absence of dissecting resorption, osteitis fibrosa, osteomalacia, and aluminium at the mineral-osteoid bone interface. Osteitis fibrosa was assessed from the degree of fibrosis in marrow cavities and graded on a five point semiquantitative scale (important osteitis fibrosa was diagnosed when fibrosis was grade 2 or higher).[26]

Hyperparathyroidism was diagnosed by an increase in the number of active bone cells (osteoblasts and osteoclasts). Osteomalacia was diagnosed by the presence of five or more osteoid lamellae as identified by birefringence under polarised light.[27] Important aluminium retention was diagnosed when stainable aluminium was identified on more than 25% of the mineral-osteoid interface. Adynamic bone lesions were diagnosed by the paucity of active bone cells, a normal or decreased osteoid seam width, and a pronounced decrease in the rate of bone formation (<0·001 mm^2/mm^3/day).

Quantitative histomorphometry was carried out with a semiautomated digitising system (OsteoMeasure, OsteoMetrics, Atlanta) and a dedicated microcomputer. Bone volume (as percentage of tissue volume), osteoid volume (as percentage of tissue volume), osteoid surface (as percentage of bone surface), osteoblast surface (as percentage of bone surface), number of osteoblasts per mm^2 of tissue area, osteoid thickness (mm), eroded surface (as percentage of bone surface), osteoclast surface (as percentage of bone surface), number of osteoclasts per mm^2 of tissue area, mineral apposition rate (mm/day), mineralising surface (as percentage of osteoid surface), and bone formation rate (mm^2/mm^3/day) were measured, and the mineralisation surface was calculated as the double labelled surface plus one half of the single labelled surface.[27] The standardised recommended nomenclature for bone histomorphometry was used.[28]

Quantitative histology of bone, the primary criterion of efficacy, was undertaken in all patients with adequately paired bone biopsies, and histological abnormalities compared between the treatment groups at the start of the study and at its end (at two years or on withdrawal from the study). For sequential biochemical assessment, all values were used to show changes with time.

STATISTICAL ANALYSIS

Statistical significance of the histological changes were evaluated by analysis of variance for treatment and centre effects and any interaction. Biochemical changes were assessed by analysis of variance to determine the significance of the treatment effect, the effect of time and any interaction. Measurements made on nominal scales (such as histological assessments and radiographic responses) were compared with χ^2 tests.

Results

INITIAL ASSESSMENT

As expected, most of the 176 patients studied had ormal serum biochemistry except for impaired renal function. However, serum phosphate and parathyroid hormone concentrations were raised in 50 and 72 patients respectively, and 132 patients were retrospectively found to have one or more histological abnormality of bone at the start of the study. Of these patients, 98 had important osteitis fibrosa, 25 had osteomalacia usually in combination with osteitis fibrosa, and one patient had osteomalacia alone. Aluminium was present at the mineral-osteoid interface in five (2%) of the biopsy specimens, and in none of these did it cover more than 25% of this surface. Nine patients had adynamic bone lesions at the start of the study. The 44 patients with no important histological abnormalities had a significantly higher mean rate of creatinine clearance compared with patients with significant bone pathology (35·9 (SD 1·7) ml/min *v* 30·8 (1·2) ml/min respectively, $P < 0.03$).

At the start of the study, nine of the patients had mild bone pain, four had borderline elevation of serum alkaline phosphatase activity, and seven had important subperiosteal erosions (retrospectively assessed). In addition, three of the patients given alfacalcidol and one given placebo had a creatinine clearance slightly in excess of 50 ml/min, and 13 patients given alfacalcidol and nine patients given placebo were receiving more than 0·5 g of calcium supplements a day. None of these patients was excluded from analysis.

BASELINE COMPARABILITY OF TREATMENT GROUPS

There were no differences in age, sex distribution, distribution of primary renal disease, or degree of renal impairment between the 89 patients given alfacalcidol and the 87 patients given placebo. There was also no difference in mean height, weight, and systolic and diastolic blood pressure, and the two groups had similar biochemical, radiological, and semiquantitative histological features at the start of the study (table I). When semiquantitative and quantitative histomorphometric data were examined before treatment from patients in whom a second biopsy was taken for paired analysis (72 patients given alfacalcidol and 62 patients given placebo) there was also no difference in any variable before treatment between the groups (table II). There was also no difference in histomorphometric findings between the 124 patients who completed the study and the 10 patients who were withdrawn early because of their starting dialysis.

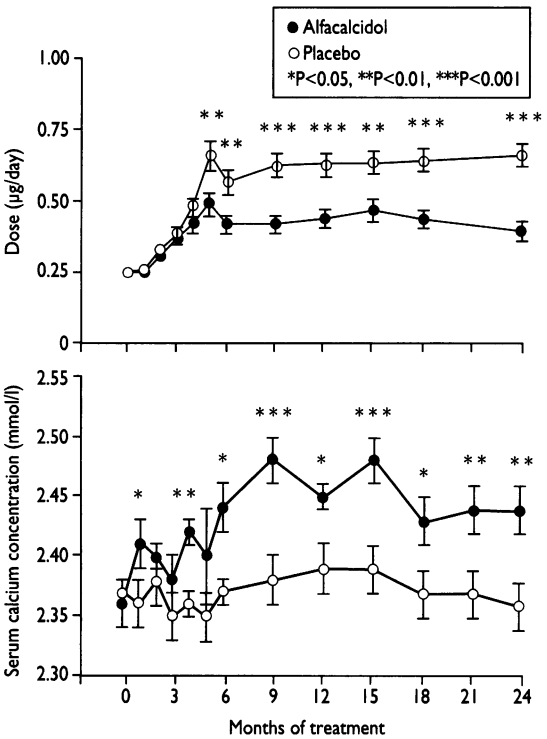
TABLE I—*Demographic, biochemical, radiological, and semiquantitative histological features at start of study for 89 patients randomised to receive alfacalcidol and 87 patients to receive placebo. Values are means (SDs) unless stated otherwise*

	Alfacalcidol (n=89)	Placebo (n=87)
Age (years)	53 (15)	51 (16)
No (%) of male patients	54 (61)	53 (61)
Renal pathology (No (%) of patients):		
Glomerulovascular	58 (65)	49 (56)
Tubulointerstitial	26 (29)	29 (33)
Unknown	5 (6)	9 (10)
Serum concentrations:		
Creatinine (mmol/l)	263 (119)	263 (127)
Corrected calcium (mmol/l)	2·36 (0·15)	2·37 (0·14)
Phosphate (mmol/l)	1·29 (0·28)	1·33 (0·33)
Alkaline phosphatase (IU/l)	154 (69)	152 (71)
Intact parathyroid hormone (pmol/l)	10·3 (15·9)	6·4 (4·6)
Urine concentrations:		
Calcium (mmol/day)	1·5 (0·8)	1·7 (1·2)
Phosphate (mmol/day)	26·8 (9·3)	25·7 (8·6)
Hydroxyproline (μmol/day)	295 (115)	276 (134)
Creatinine clearance (ml/min)	31·6 (10·8)	32·9 (11·6)
No (%) of patients with subperiosteal erosions	4 (4)	2 (2)
Histological abnormalities (No (%) of patients):		
Osteitis fibrosa	67 (75)	62 (71)
Osteitis fibrosa and osteomalacia	16 (18)	17 (20)
Osteomalacia alone	0	1 (1)
Aluminium staining of bone	2 (2)	0
Adynamic bone lesions	6 (7)	3 (3)

TABLE II—*Quantitative histomorphometry at start of study in 72 patients randomised to receive alfacalcidol and 62 patients to receive placebo. Values are means (SDs). See methods section for details of measures*

	Alfacalcidol (n=72)	Placebo (n=62)
Bone volume (%)	18·2 (7·3)	17·8 (6·9)
Osteoid volume (%)	0·57 (0·61)	0·45 (0·42)
Osteoid surface (%)	16·4 (14·5)	14·4 (12·4)
Osteoblast surface (%)	1·19 (1·69)	0·90 (1·02)
No of osteoblasts/mm²	0·73 (1·01)	0·52 (0·59)
Osteoid thickness (mm)	8·44 (1·98)	8·51 (1·92)
Eroded surface (%)	16·6 (7·5)	14·9 (7·2)
Osteoclast surface (%)	0·70 (0·75)	0·66 (0·61)
No of osteoclasts/mm²	0·17 (0·16)	0·16 (0·16)
Mineral apposition rate (mm/day)	0·58 (0·23)	0·58 (0·18)
Bone formation rate (mm²/mm³/day)	10·9 (10·6)	11·1 (11·0)
Mineralising surface (%)	33·0 (20·4)	36·2 (23·4)
Mineralisation lag time (days)	13·9 (3·7)	14·6 (4·0)

No significant difference between groups in any measurement.



Dose of alfacalcidol or placebo and corrected serum calcium concentration in 89 patients given alfacalcidol and 87 patients given placebo for 102 weeks. Points and bars indicate means and standard errors, and asterisks denote significance of differences between treatments

The two groups had similar concomitant drug treatment, which consisted mostly of antihypertensive drugs and diuretics. Similar numbers of patients were receiving glucocorticoids in both groups.

LONG TERM ASSESSMENT

The dose of alfacalcidol and placebo given increased progressively over the first six months of the study and then remained reasonably constant (figure). There was a significant difference between the dose of alfacalcidol given and that of placebo from the fourth month of the study onwards ($P < 0.001$). At the end of the study 34 (46%) of the 73 patients still taking alfacalcidol were receiving 0·25 μg daily, 22 (30%) were taking 0·5 μg, and nine (12%) were taking 1 μg. Of the 65 patients still taking placebo at the end of the study, 13 (20%), 13 (20%), and 33 (51%) were taking daily doses of 0·25 μg, 0·5 μg, and 1 μg respectively. The remaining patients received the treatment every other day or once a week.

Thirty eight patients (16 given alfacalcidol and 22 given placebo) withdrew prematurely from the study (table III). The most common cause for withdrawal was the need to start dialysis, while default and death

(mainly due to cardiovascular disease) were the other main causes. Reported side effects included mild gastrointestinal disturbances (six patients given alfacalcidol and one given placebo) and pseudogout (two patients given alfacalcidol). These were mild, and none of the patients was withdrawn from the study because of side effects, persistent hypercalcaemia, or unexpected progression of renal failure.

BIOCHEMICAL RESPONSE

There was a small but significant increase in corrected serum calcium concentration in the patients given alfacalcidol; this was evident at the first assessment at four weeks after the start of treatment and persisted for the duration of treatment. There was no significant change in patients taking placebo (table IV, figure). During the study, three patients given placebo and 10 patients given alfacalcidol developed mild hypercalcaemia (P=0·09)—in the patients given alfacalcidol this responded to a decrease in drug dose. Severe hypercalcaemia (corrected serum calcium concentration >3·00 mmol/l) was observed on one occasion in four patients taking alfacalcidol (table III). Mean 24 hour urinary calcium excretion increased in the patients receiving alfacalcidol but not in those taking placebo (table IV). (The changes in urine calcium excretion observed in the alfacalcidol treated group suggest that most of the patients evaluated were compliant with treatment.)

Mean serum phosphate concentration increased in both groups, and there was no significant difference between the two groups in mean changes in serum concentrations at any time during the study (table IV). Of the patients taking calcium supplements, only one in each group required phosphate binding drugs that contained aluminium to control serum phosphate concentration. Two others (one in each group) were taking aluminium based compounds as antacids. There was no significant difference between the two groups in urinary phosphate excretion, but hydroxyproline excretion was significantly decreased at the end of the study in the patients taking alfacalcidol compared with those taking placebo (table IV).

TABLE III—*Reasons for premature withdrawal from study and incidence of intercurrent hypercalcaemia in 89 patients randomised to receive alfacalcidol and 87 patients to receive placebo. Values are numbers (percentages)*

	Alfacalcidol (n=89)	Placebo (n=87)	P value
Withdrawals:	16	22	0·24
Dialysis	8	10	
Death	4	1	
Hypocalcaemia	0	1	
Hypercalcaemia	0	0	
Other (default, etc)	4	10	
Intercurrent hypercalcaemia (serum calcium):			
2·63-3·00 mmol/l	10 (11)	3 (3)	0·09
>3·00 mmol/l	4 (4)	0	

The group given alfacalcidol showed a small, non-significant decrease in serum concentrations of parathyroid hormone after six months of treatment and then a slow rise so that, at the end of two years, parathyroid hormone concentrations were the same as before treatment. In contrast, the group given placebo showed a significant, progressive, twofold increase in concentrations of parathyroid hormone (table IV). The changes in serum activity of alkaline phosphatase were similar to those observed with serum parathyroid hormone concentrations in both groups. Thus, in patients given alfacalcidol, alkaline phosphatase activity decreased by 15% in the first six months of treatment, remained so for most of the duration of treatment, but had risen to pretreatment values by the end of the study. In the group given placebo, enzyme activity significantly and progressively increased and was significantly higher than in the alfacalcidol treated group at the end of treatment (table IV).

In both groups renal function declined progressively, and this reduction was significant by the end of the study. There was, however, no significant difference between the groups in the reduction in renal function, serum creatinine concentration, and endogenous creatinine clearance, as calculated by the standard or by the Cockcroft method, at the end of the study.

RADIOLOGICAL RESPONSE

There was no significant change in subperiosteal erosions during the study and no significant difference between the groups. Measurements of combined cortical width decreased equally and non-significantly in both groups.

HISTOLOGICAL RESPONSE

At the end of the study 134 pairs of biopsy specimens were available for analysis (124 after two years and 10 on withdrawal from the study after 5-17 months of treatment to start dialysis). These paired specimens came from 72 of the patients given alfacalcidol and 62 of the patients given placebo. The proportions of these patients with bone abnormalities at the start of the study were similar: 55 (76%) of those taking alfacalcidol and 45 (73%) of those taking placebo. At the end of the study, however, these proportions had changed to 54% (39) of those taking alfacalcidol and 82% (51) of those taking placebo.

In the minority of patients with apparently normal bone histology at the start of the study there was no significant difference in bone histology at the end of the study between those given alfacalcidol and those given placebo (P=0·73). In contrast, among patients with histological abnormalities at the start of the study, 23

TABLE IV—*Changes in biochemical and radiographic features between start of study and after 6, 12, 18, and 24 months in 89 patients given alfacalcidol and 87 patients given placebo. Values are means (standard errors)*

	Months of treatment with alfacalcidol				Months of treatment with placebo				P values*	
	6	12	18	24	6	12	18	24	Treatment	Time
Serum concentrations:										
Creatinine (μmol/l)	32·3 (7·2)	57·6 (14·0)	59·3 (12·1)	78·8 (15·6)	26·8 (8·2)	39·6 (9·4)	44·2 (11·7)	74·1 (18·7)	0·41	<0·001
Corrected calcium (mmol/l)	0·08 (0·02)	0·08 (0·02)	0·07 (0·02)	0·07 (0·02)	0·00 (0·01)	−0·01 (0·02)	−0·01 (0·03)	−0·01 (0·03)	<0·001	0·91
Phosphate (mmol/l)	−0·04 (0·03)	−0·04 (0·03)	0·00 (0·03)	0·13 (0·05)	−0·04 (0·03)	−0·04 (0·03)	−0·06 (0·04)	−0·06 (0·06)	0·48	<0·001
Alkaline phosphatase (IU/l)	−25·5 (5·2)	−23·3 (6·1)	−18·4 (6·9)	−5·7 (6·8)	−8·1 (4·7)	0·8 (4·5)	12·6 (6·1)	19·8 (6·6)	<0·001	<0·001
Intact parathyroid hormone (pmol/l)	−2·9 (1·7)	−1·6 (0·9)	−1·6 (1·2)	0·6 (1·0)	2·0 (0·6)	5·9 (1·2)	7·3 (1·4)	8·1 (2·1)	<0·001	<0·001
Creatinine clearance (ml/min)	−1·3 (1·2)	−3·5 (1·4)	−3·5 (1·7)	−5·7 (1·0)	−3·1 (1·0)	−3·3 (1·4)	−2·8 (1·6)	−4·0 (2·0)	0·94	0·03
24 Hour urine excretion†:										
Creatinine (mmol/day)	−0·96 (07·1)	−1·28 (0·72)	−1·19 (0·62)	−1·87 (0·52)	−1·14 (0·55)	−0·42 (0·46)	−0·05 (0·79)	−0·82 (0·68)	0·36	0·06
Calcium (mmol/day)	0·47 (0·19)	0·80 (0·26)	0·70 (0·27)	0·87 (0·27)	0·36 (0·50)	−0·08 (0·24)	−0·07 (0·25)	0·56 (0·35)	0·06	0·72
Phosphate (mmol/day)	−2·74 (1·67)	−3·52 (1·73)	−5·46 (1·89)	−5·73 (1·48)	−2·69 (1·88)	−1·86 (1·51)	−1·98 (2·01)	−2·82 (1·76)	0·34	0·02
Hydroxyproline (μmol/day)	−93·7 (21·4)	−69·0 (21·6)	−84·4 (23·4)	−62·1 (23·4)	−57·7 (29·5)	−25·7 (27·7)	−27·3 (26·6)	10·7 (23·6)	0·09	0·84

* One centre only: 36 patients given alfacalcidol, 35 patients given placebo.
† Significance of differences between treatments and significance of changes with time measured by analysis of variance (treatment *v* time interaction was not significant in all cases).

TABLE V—*Semiquantitative and quantitative histological changes at the end of the study in 72 patients given alfacalcidol and 62 patients given placebo according to whether histological abnormalities were present at start of study. Values are means (standard errors)*

	Histological abnormalities at start of study			No histological abnormalities at start of study		
	Alfacalcidol (n=55)	Placebo (n=45)	P value†	Alfacalcidol (n=17)	Placebo (n=17)	P value†
Semiquantitative changes (% of patients affected):						
Degree of fibrosis	−0·58 (0·1)***	0·07 (0·1)	0·0002	0·53 (0·2)**	0·59 (0·2)**	0·88
Maximum No of osteoid lamellae	−0·73 (0·2)***	0·32 (0·2)	0·002	0·35 (0·5)	0·18 (0·3)	0·47
Quantitative changes‡:						
Bone volume (%)	1·22 (0·9)	1·09 (1·1)	0·75	0·29 (2·2)	0·83 (1·7)	0·9
Osteoid volume (%)	−0·30 (0·1)***	0·09 (0·1)	0·005	0·10 (0·1)	0·14 (0·1)	0·2
Osteoid surface (%)	−6·85 (1·8)**	1·35 (1·6)	0·008	0·44 (2·5)	0·80 (3·1)	0·2
Osteoblast surface (%)	−0·54 (0·3)**	0·37 (0·3)	0·009	0·58 (0·2)*	0·40 (0·2)	0·3
No of osteoblasts/mm² (%)	−0·38 (0·1)**	0·24 (0·2)	0·007	0·33 (0·1)*	0·20 (0·1)	0·26
Osteoid thickness	−0·49 (0·4)	0·05 (0·4)	0·37	−0·22 (0·4)	2·10 (0·6)**	0·004
Eroded surface (%)	−3·76 (1·1)***	0·45 (0·9)	0·04	−1·06 (1·9)	4·50 (2·3)	0·054
Active eroded surface (% of bone surface)	−0·86 (0·5)	0·49 (0·3)	0·0006	0·56 (0·4)	0·26 (0·4)	0·76
Osteoclast surface (%)	−0·30 (0·2)	0·17 (0·1)	0·002	0·16 (0·1)	0·03 (0·1)	0·51
No of osteoclasts/mm²	−0·07 (0·04)	0·05 (0·03)	0·001	0·04 (0·03)	0·01 (0·03)	0·76
Mineral apposition rate (mm/day)	−0·05 (0·04)	0·01 (0·04)	0·34	0·05 (0·1)	−0·03 (0·1)	0·53
Bone formation rate (mm²/mm³/day)	−4·66 (1·9)*	0·51 (1·7)	0·15	6·29 (4·5)	3·91 (2·4)	0·65
Mineralising surface (% of bone surface)	−1·99 (0·8)*	−0·15 (0·6)	0·16	2·35 (1·8)	1·60 (0·9)	0·59
Mineralising surface	2·68 (3·5)*	−3·41 (2·6)	0·26	14·55 (8·8)	−2·63 (8·9)	0·22
Mineralisation lag time (days)	−0·75 (0·8)*	−9·56 (0·8)	0·93	−2·55 (1·3)	2·07 (2·1)	0·05

* P<0·05, **P<0·01, ***P<0·001; differences within treatment groups.
† Differences between treatment groups.
‡ See methods section for details of measures.

(42%) of the patients given alfacalcidol showed normal histological appearances at the end of the study compared with only two (4%) of those given placebo (P<0·001). Table V shows that the patients with pre-existing histological abnormalities who were treated with alfacalcidol showed improvements in hyperparathyroid bone disease in terms of a decrease in the severity of marrow fibrosis and a decrease in bone turnover as indicated by a significant decrease in histological indices of bone resorption (including the eroded surface and active eroded surface) and a decrease in indices of bone formation (including the number of osteoblasts, osteoblast surface, and osteoid surface and volume). Osteomalacia, though uncommon, also improved, as indicated by a decrease in the maximum number of osteoid lamellae and in the osteoid thickness. In the group given placebo these histological indices tended to worsen (table V). No significant differences were seen between centres in the histological responses recorded.

At the end of the study adynamic bone lesions had resolved in four of the six patients taking alfacalcidol who had been affected at the start of the study and in two of the three patients taking placebo. Adynamic bone lesions developed in eight patients given alfacalcidol and in four patients given placebo. None of the patients with adynamic bone lesions at the start or end of the study had positive staining for aluminium at the mineral-osteoid interface. At the end of the study aluminium staining was no longer present in the two patients taking alfacalcidol in whom it had been present at the start of the study, but it appeared in one other patient taking alfacalcidol and in two patients taking placebo.

Discussion

This is the first prospective, double blind, placebo controlled study to examine the long term effects of alfacalcidol on the natural course of bone disease in patients with early renal failure. It is also the largest long term study of any hydroxylated metabolite of vitamin D in patients with impaired renal function. Our findings suggest that early administration of alfacalcidol can safely and beneficially alter the natural course of renal bone disease in patients with mild to moderate impairment in renal function. Thus, whereas the patients given placebo showed a sustained deterioration in biochemical and histological indices of bone metabolism, those given alfacalcidol showed a significant improvement in bone histology.

It is evident, however, that most of the patients had renal bone disease at the time of entry to the study, despite normal serum activity of alkaline phosphatase and normal radiographic findings. Forty per cent of the patients had raised concentration of parathyroid hormone, but this was shown only on retrospective analysis at the end of the study. It is well established that biochemical and radiographic indices are less sensitive than bone histology in patients with renal failure,[4 29 30] and our findings support this. Because of the high prevalence of histological abnormalities, the main result of our study is that subclinical bone disease is improved by alfacalcidol, rather than that the treatment provides true prophylaxis for renal bone disease. Thus the main benefit of long term treatment is likely to be to delay the start of clinically important bone disease.

Despite the maintenance of serum calcium concentrations at the upper limit of laboratory reference range during treatment with moderate doses of alfacalcidol, mean serum alkaline phosphatase activity and parathyroid hormone concentration at the end of the study were not significantly different from those at the start. There was, however, a decrease in serum parathyroid hormone concentration and alkaline phosphatase activity after six months of treatment, followed by a later rise to pretreatment values. This "escape" pattern is similar to that seen in the treatment of renal bone disease with active derivatives of vitamin D in patients receiving haemodialysis.[31 32] The lack of sustained effect of alfacalcidol on these biochemical indices of bone metabolism suggests that factors other than the maintenance of a normal serum calcium concentration and the correction of 1,25-dihydroxycholecalciferol deficiency also play an important part in the control of parathyroid hormone secretion in patients with impaired renal function.

POTENTIAL HAZARDS OF TREATMENT

The potential hazards of long term treatment with alfacalcidol include inappropriate suppression of bone turnover resulting in "adynamic bone lesions," characterised histologically by a paucity of bone cells and a substantial decrease in bone formation. The clinical importance of adynamic bone lesions is not known; in our study they developed in 12 patients during treatment, but they also resolved in six of the nine patients in whom they had been present before treatment. This suggests that the long term use of alfacalcidol does not represent a significant risk for adynamic bone lesions.

Key messages

- About three quarters of patients with mild to moderate renal failure have histological evidence of bone disease.
- Treating such patients with alfacalcidol (up to 1 μg/day for two years) significantly improved their osteomalacia and hyperparathyroid disease
- Treatment had no apparent adverse effect on renal function
- Hypercalcaemic episodes were uncommon and readily responded to decreases in drug dose
- Alfacalcidol might be used more widely for patients with moderate renal failure not yet needing dialysis

The main concern raised about long term use of vitamin D derivatives in patients with impaired renal function is the risk of inducing or accelerating the progression of renal failure. We did not observe a more rapid decline in renal function in the patients given alfacalcidol than in those given placebo despite the consistent increment in serum calcium concentration and the increase in the urinary excretion of calcium that the treatment caused. Hypercalcaemic episodes were uncommon and were readily reversible by decreasing the daily dose of alfacalcidol. Changes in serum creatinine concentration not associated with changes in creatinine clearance have been reported in elderly patients treated with vitamin D metabolites, possibly as a result of changes in muscle mass.[34] This was not seen in our group of patients, in whom changes in serum creatinine concentration paralleled those in creatinine clearance. Our data therefore do not support the notion that the long term use of alfacalcidol has a deleterious effect on renal function.

CONCLUSION

We conclude that renal bone disease is common in patients with a creatinine clearance of 15-50 ml/min and that the use of tolerable doses of alfacalcidol to a maximum of 1 μg/day results in a substantial improvement in skeletal lesions and thereby favourably alters the natural course of bone disease. The high prevalence of bone disease in patients with early renal failure and the safety and efficacy of the regimen we used suggest that alfacalcidol might be more widely used in the management of patients with asymptomatic bone disease before dialysis is required. In addition, hyperparathyroidism with impaired renal function is probably a contributing factor to bone loss in elderly people,[35] so the use of alfacalcidol to prevent hip fractures is worthy of investigation.

Since bone disease is common, even with moderate degrees of renal impairment, and since we observed no adverse skeletal effects of treatment, bone biopsy is not normally required either to start treatment or to monitor its effects. We found no adverse effects of alfacalcidol on renal function, but hypercalcaemia occurred more often among patients given alfacalcidol than among patients given placebo. Prolonged hypercalcaemia should be avoided, so that serum calcium concentration should be monitored. We suggest that calcium concentration should be monitored monthly for the first six months of treatment and then every three months, but patients should be recalled and their dose adjusted if they develop hypercalcaemia.

We thank all colleagues who referred patients to our study; Mrs N Downes, Leo Labs UK, for coordinating the study; Dr S Woodhead, Cardiff University Hospital, for performing the assays for parathyroid hormone; and Drs M Aparicio, P Aubert, J Chanard, J-F de Fremont, B Hory, M Labbeeuw, P Rieu, P Simon, M Tolani, M Dratwa, B George, and N Lameire for contributing to the study. Statistical analysis was performed centrally at Leo Labs UK and Denmark by I Fairey, N Underwood, and C Bay. NATH is now chef de clinique, Metabolic Bone Unit, University Hospital, Leiden, Netherlands.

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(Accepted 25 November 1994)