

Effect of low dose 1α -hydroxycholecalciferol on glomerular filtration rate in moderate renal failure

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SUMMARY Serial measurements of ^{51}Cr edetic acid clearance were made over a period of one year in two groups of 8 children, in a double blind trial of 1α -hydroxycholecalciferol (10 ng/kg/day) and calciferol (670 ng/kg/day). Glomerular filtration rate (GFR) at the beginning of the trial was 20–50 ml/min/1.73 m²; it rose in the children given 1α -hydroxycholecalciferol (group A) after 6 months but was not appreciably different from the pretreatment value after 12 months. The ^{51}Cr GFR in the children given calciferol (group B) showed no significant difference at 6 or 12 months. Parathyroid hormone values fell markedly in group A after 6 months but not in group B. Quantitative bone histology improved considerably in group A but not in group B at 12 months.

Low dose 1α -hydroxycholecalciferol may be used effectively for renal osteodystrophy in children with moderate but stable renal failure without jeopardising renal function.

It has been suggested that 1α -hydroxycholecalciferol (1α OHCC) may cause deterioration in renal function in patients with advanced renal failure.^{1–4} 1α OHCC remains the most available of the potent vitamin D analogues but some clinicians limit its use to severe symptomatic renal bone disease because of the risk of deterioration in renal function.^{3 5 6} Nielson⁵ studied for 6 months the effects of 1α OHCC on 9 patients with advanced renal failure who had not received dialysis. He noted improvement in histological and biochemical signs of renal osteodystrophy but an appreciable fall in renal function. Compston⁷ studied the effects of short term administration of 1α OHCC (1 μg daily) on patients with normal renal function and found no adverse effects on GFR. To date, however, there has been no long term study of low dose 1α OHCC in patients with moderate renal impairment, the stage at which over 60% of patients show raised parathyroid hormone (PTH) values, and over 50% histological evidence of mild to moderate renal osteodystrophy.⁸ Early treatment may prevent subsequent bone deformities and tertiary hyperparathyroidism and we therefore studied the long term effects of 1α OHCC on renal function in these patients.

Patients and methods

Sixteen children aged 6½ to 18 years (mean 10.4 years) with moderately impaired but stable renal function (GFR, 20–50 ml/min/1.73 m²) were

entered into a year long double blind trial of 1α OHCC 10 ng/kg/day (group A) and calciferol 670 ng/kg/day, (group B). Calciferol was used as 'placebo' for ethical reasons for all patients undergoing bone biopsy after one year on 'treatment'. Patients previously treated with vitamin D or its analogues were excluded from the survey. One patient was on propranolol and two were on aludrox at the beginning of the trial. Aludrox was used subsequently during the trial to keep serum phosphate below 1.8 mmol/l (5.6 mg/100 ml). Informed parental consent was obtained in all cases.

^{51}Cr edetic acid (EDTA) slope clearance was estimated at the beginning of the study and subsequently at 6 and 12 months using venous samples taken at 0, 15, 60, 90, and 120 minutes, according to the method of Brøchner-Mortensen *et al.*⁹ Serum calcium, phosphate, and creatinine were measured fortnightly for the first three months and thereafter at monthly intervals on an automated continuous flow analyser employing the Jaffe reaction. PTH was measured by a radioimmunoassay that detects primarily the 'C' terminal component, which is the inactive fragment. A full skeletal survey was made at the beginning of the study and hand and wrist radiographs and estimation of bone mineral density were carried out at 6 monthly intervals. Quantitative bone histology was done on transilial bone biopsies taken at the beginning and end of the study from the posterior iliac spine with a 13 gauge Jamshidi needle. The significance of results between the

groups was assessed by the Mann-Whitney U test, and for paired comparisons, the Wilcoxon's rank sum test.

Results

⁵¹Cr EDTA clearance showed no significant difference between the groups at the beginning of the survey (Fig. 1). There was a significant rise in GFR

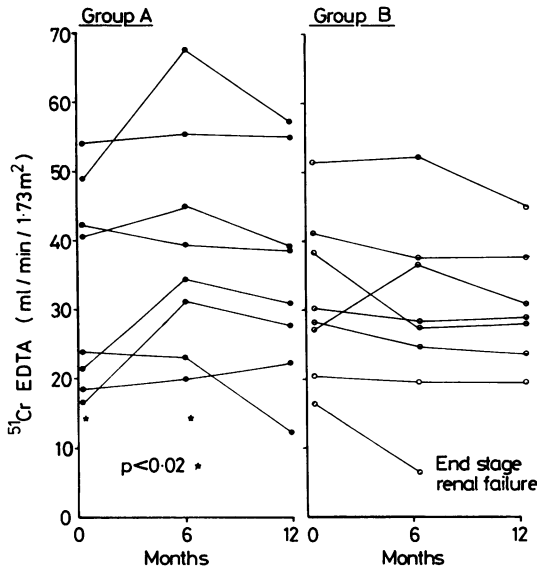


Fig. 1 ⁵¹Cr edectic acid clearance ml/min/1.73 m² before and during treatment with 1 α -hydroxycholecalciferol (group A) or calciferol (group B).

P is for paired student's *t* test and is indicated where significant.

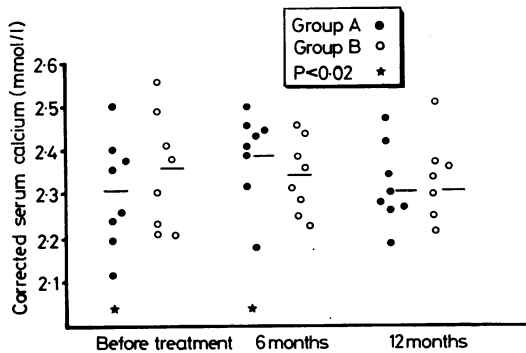


Fig. 2 Changes in serum calcium values in group A patients treated with 1 α -hydroxycholecalciferol and in group B patients treated with calciferol.

P values are indicated where significant and are for student's *t* test.

in group A at 6 months, P<0.02. One patient in group B went into end stage renal failure at 7 months (GFR <5 ml/min/1.73 m²) and was withdrawn from the study. The two groups were comparable at 12 months with no significant difference between them.

Serial measurements of serum calcium corrected for albumin are given in Fig. 2. There were no episodes of hypercalcaemia during the study. Serum calcium rose significantly from the pre-treatment value in group A at 6 months, P<0.02. There was no similar rise on group B but the groups were comparable at 12 months.

Serum phosphate rose significantly in group A at 3 months P<0.02 (Fig. 3) and four patients in this group required aluminium hydroxide. Despite the aluminium hydroxide, however, there was a significant difference between the two groups at 12 months, with higher values in group A, P<0.05.

PTH values are given in Fig. 4. PTH was suppressed significantly at 6 months by 1 α OHCC, P<0.01, but rose subsequently at 12 months with no significant difference between the two groups at that time.

Total serum alkaline phosphatase, alkaline phosphatase bone isoenzyme, urine calcium/creatinine ratio, and bone mineral density showed no significant difference between or within the groups throughout the study.

Two patients in group A and one in group B had radiological evidence of hyperparathyroidism with subperiosteal erosions over the middle phalanges at the beginning of the trial. Repeat bone radiographs were normal in the two patients in group A at 6 and 12 months, but showed deterioration of the hyperparathyroid lesions in the patient in group B. In group A 62.5% had abnormal bone histology with woven osteoid, increased osteoid seams, and trabecular osteoid volume at the beginning of

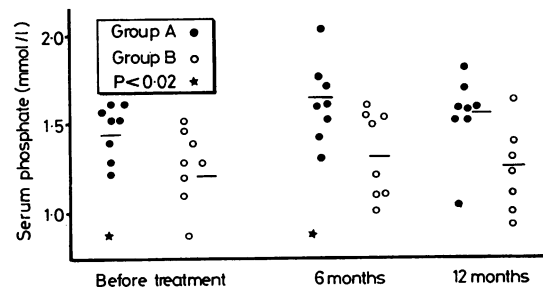


Fig. 3 Changes in serum phosphate values in group A patients treated with 1 α -hydroxycholecalciferol and group B patients treated with calciferol.

P values are for paired student's *t* test and are indicated where significant.

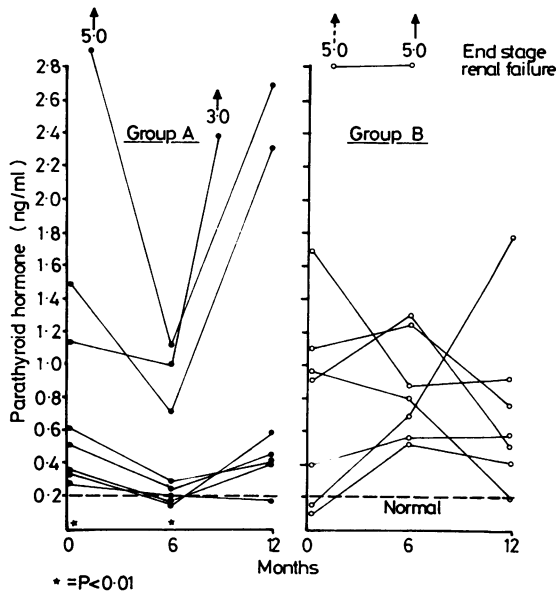


Fig. 4 Parathyroid hormone values in group A and group B patients. Normal values are less than 0.2 ng/ml.

P is for paired student's *t* test.

treatment, and 12.5% at the end. In group B 62.5% had abnormal bone histology before and after treatment (difference between groups $\chi^2=4.3$; $P=0.04$).

Discussion

Tougaard and Sørensen in 1976¹ and our group in Birmingham in 1978² suggested various reasons for the fall in GFR noted in patients on treatment with 1α OHCC. The first, hypercalcaemia, was not seen in any of the patients in this study. The second reason is hyperphosphataemia which was adequately controlled with aluminium hydroxide in our patients. The third is absence of vitamin D metabolites, possibly 24, 25 dihydroxyvitamin D, for which no real evidence is available. Fourthly, it has been suggested that suppression of PTH may lead to a fall in renal blood flow.¹⁰ PTH was significantly suppressed by 1α OHCC in this study at 6 months ($P=0.01$) without a fall in GFR, and this eliminates the last hypothesis.

Previous reports showing deterioration in renal function associated with 1α OHCC have studied patients with advanced or end stage renal failure.^{1-6 11} To date, however, there has been no long term study of the effects of 1α OHCC on renal

function in patients with moderate renal impairment. Farrington¹² and Feest¹³ studied patients with advanced renal failure treated with 1α OHCC and noted no important deterioration in renal function. Pierides¹⁴ found no deterioration in 7 uraemic patients treated with 1α OHCC, other than that associated with the natural progression of the disease. Malluche *et al.*¹⁵ treated three adult patients, with mild to moderate renal impairment, with 0.5 μ g 1α OHCC daily for 6 months. They all had abnormal bone histology before treatment, but after there was complete healing of the osteopathy. No reference was made, however, to the state of their renal function after treatment.

The patients in this study had moderate but stable renal function that showed no deterioration during 1α OHCC treatment. It is possible that the effect of 1α OHCC on renal function is related to the severity of renal impairment at the start of treatment and patients with moderate but stable renal function may not therefore be as adversely affected as those with severe renal impairment.

One patient in group A had an appreciable fall in GFR after 7 months of treatment, but this subsequently returned to near pretreatment value with no change in treatment. This patient had been on propranolol which was stopped after three months on 1α OHCC because of profound bradycardia. He was not hypertensive nor was there any evidence of intercurrent infection when his serum creatinine concentration rose. It is possible that the sudden rise in his serum creatinine and PTH values was secondary to the withdrawal of the protective effect of beta blockers on the parathyroid glands.^{16 17}

The PTH value was considerably suppressed by 1α OHCC at 6 months in group A. Although the fall in PTH occurred during the summer months, no corresponding fall was noted in group B patients treated simultaneously but with calciferol. PTH suppression noted in this study confirms the observations made by Canterbury *et al.*¹⁸ In their experiments with mongrel dogs, direct infusion of equal doses of 1,25-hydroxycholecalciferol and 24,25-dihydroxyvitamin D into the parathyroid glands caused complete suppression of PTH. PTH rose subsequently at 12 months in group A—this may reflect the corresponding fall of the mean dose of 1α OHCC to 8.75 ng/kg/day, caused partly by growth and weight gain among the patients and partly by non-compliance noted in one patient in group A at that time.

The rise in PTH is unlikely to be caused by a 'breakthrough' phenomenon noted by Kanis *et al.*¹¹ on doses of 1α OHCC found to be previously effective, as bone histology had returned to normal

despite the rise in PTH that probably precedes abnormal histology. It is likely that less than 10 ng/kg/day of 1 α OHCC is insufficient for continued suppression of PTH.

In group A serum calcium rose significantly at three and 6 months (P<0.014 and P<0.02, respectively), but there were no episodes of hypercalcaemia during the survey. This suggests that 1 α OHCC in a dose of 10 ng/kg/day carries little risk of hypercalcaemia and obviates the need to monitor frequently serum calcium in patients treated with such doses.

In conclusion, if serum phosphate is kept within normal values, low dose 1 α OHCC may be used effectively to heal renal osteodystrophy in patients with moderately impaired but stable renal function, with little risk of deterioration in GFR.

We thank Dr R H R White for permission to include his patients in this study, Dr C Edwards and the Department of Histopathology, East Birmingham Hospital for processing the bone biopsies, Dr C Carter and Miss A Horton for ⁵¹Cr EDTA assays, Dr D A Heath for serum parathyroid hormone assays, Dr P Robertson for x-rays and bone mineral assays, Mrs D Frewin for her help in preparing the manuscript, and Mr N Underwood of Leo Laboratories for supplying 1 α OHCC and calciferol.

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Received 20 June 1983