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1α-Hydroxycholecalciferol: A Treatment for Renal Bone Disease

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Summary

Three patients with chronic renal failure on maintenance haemodialysis have been treated with 1α-hydroxycholecalciferol (1α-OHCC), a synthetic vitamin D analogue. A daily dose of 2 μg by mouth produced a significant increase in both calcium absorption from the gastrointestinal tract and calcium content of bone. Treatment with 1α-OHCC appears to be effective in cases of metabolic bone disease associated with chronic renal failure.

Introduction

It has been known for more than a century that patients with renal failure may develop metabolic bone disease (Virchow, 1855; Lucas, 1883). The importance of this association has been appreciated only since advances in treatment have extended life expectancy and shown that bone disease is an important factor in limiting the full rehabilitation of many patients (Ogg, 1973). Though it was found that large doses of vitamin D could produce a marked improvement in the osteodystrophy of patients with chronic renal failure the dangers of vitamin D toxicity—prolonged hypercalcaemia, metastatic calcification, and nephrocalcinosis—were considerable (Stanbury, 1957; Dent *et al.*, 1961; Fletcher *et al.*, 1963).

In 1970 Fraser and Kodicek discovered that a potent metabolite of vitamin D was produced in the kidney. This substance, 1,25-dihydroxycholecalciferol, was shown subsequently to stimulate calcium absorption in nephrectomized animals (Boyle *et al.*, 1972). It is not detectable in the serum of anephric animals (DeLuca, 1973 a) or in the serum of patients with chronic renal insufficiency (Mawer *et al.*, 1973). 1,25-Dihydroxycholecalciferol is more polar, less lipid soluble, and more potent than vitamin D. Brickman and Norman (1973) suggested that when it is administered to patients with evidence of vitamin D deficiency the lower dosages required and the reduced tissue stores may limit the toxic effects of inadvertent overdosage.

Though radiological improvement in renal osteodystrophy has been shown after treatment with 1,25-dihydroxycholecalciferol (Henderson *et al.*, 1974) this drug is unlikely to become generally available in the near future because of technical difficulties in its production (DeLuca, 1973 b). An analogue of vitamin D has been synthesized with a hydroxyl group at carbon-1. This substance, 1α-hydroxycholecalciferol (1α-OHCC), which may bypass the renal hydroxylating mechanism, is relatively simple to produce (Harrison *et al.*, 1973), has the same antirachitic activity as vitamin D, and promotes both calcium absorption from the gastrointestinal tract and calcium mobilization from bone (Holick *et al.*, 1973). It is effective at doses similar to those of 1,25-dihydroxycholecalciferol and functions equally well in anephric animals and animals with intact kidneys (DeLuca, 1973 a). The administration of 1α-OHCC parenterally (Chalmers *et al.*, 1973) and by mouth (Peacock *et al.*, 1974) has been shown to increase calcium absorption in patients with renal insufficiency.

The present study was undertaken to evaluate the effect of 1α-OHCC on the progressive osteodystrophy of three patients with chronic renal failure on maintenance haemodialysis.

Patients and Methods

All three patients gave informed consent to the investigation. None had symptomatic bone disease.

CASE HISTORIES

Case 1.—A 33-year-old man with hypoplastic kidneys started maintenance haemodialysis in March 1967. Small subperiosteal erosions were noted radiologically in 1972 and these remained unchanged; there was no further radiological evidence of metabolic bone disease. Bone biopsy showed increased osteoblastic and osteoclastic activity with wide osteoid seams and fibrosis of the marrow cavity. During the period of study his diet contained approximately 272 mg calcium and 616 mg phosphorus a day.

Case 2.—This patient, a 46-year-old man diagnosed as having chronic pyelonephritis, started maintenance haemodialysis in February 1969. Repeated radiological skeletal surveys showed only a slight diminution of bone density but a bone biopsy showed marrow fibrosis and wide osteoid seams. During the study his diet contained 269 mg calcium and 706 mg phosphorus a day.

Case 3.—A 43-year-old man with chronic glomerulonephritis started maintenance haemodialysis in June 1969. Though repeated skeletal surveys failed to detect any evidence of bone disease a bone biopsy showed wide osteoid borders, an increase in both osteoblastic and osteoclastic activity, and marrow fibrosis. His diet contained 374 mg calcium and 648 mg phosphorus a day.

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TREATMENT

Standard Kiil dialysers with a surface area of 1 m^2 were used; the patients were dialysed for 28 hours a week and the dialysis fluid, prepared by diluting a concentrate with mains tap-water, contained calcium in a concentration of 1·5 mmol/l. Magnesium to a final concentration of 0·8 mmol/l. was added to the dialysate in case 1. All three patients received a daily dietary supplement of 2 g calcium as calcium carbonate and none received aluminium hydroxide.

INVESTIGATIONS

Calcium was measured by an automated cresol saline method; phosphate was determined by the vanadate method (Davies *et al.*, 1973). Bone biopsy specimens were obtained by a modification of the technique of Williams and Nicholson (1963). Cylinders of bone were taken from the left iliac crest and prepared for histological examination by the method of Tripp and MacKay (1972).

The absorption of calcium was measured before and after treatment with 1α-OHCC by a modification of the forearm counting method (Pak *et al.*, 1972). The mean of counts made over the skull and both legs four and 24 hours after the oral administration of 2·5 μCi ^{47}Ca was recorded; 100 mg stable calcium as calcium chloride was given with the oral dose. Seven days later 2·5 μCi ^{47}Ca was injected intravenously and the counting procedure repeated. All tests of calcium absorption were performed two to four hours after a dialysis treatment. The results (tables I and II) are expressed as count ratios (oral : intravenous).

TABLE I—*Results of Calcium Absorption Test Expressed as Count Ratios (Oral: Intravenous)*

Case No.	1α-OHCC		Calcium Absorption (%) (Mean ± S.E.)		P
	Dose (μg/Day)	Time (Days)	Control	Treatment	
1.. ..	2	22	28 ± 4	43 ± 2	<0·005
2.. ..	2	20	30 ± 3	68 ± 3	<0·001
3.. ..	2	13	53 ± 2	78 ± 3	<0·001

TABLE II—*Results of Repeated Calcium Absorption Tests Expressed as Count Ratios (Oral: Intravenous)*

Case No.	1α-OHCC		Calcium Absorption (%) (Mean ± S.E.)		P
	Dose (μg/Day)	Time (Weeks)	Control	Treatment	
1.. ..	2	9	28 ± 4	85 ± 6	<0·001
2.. ..	2	9	30 ± 3	73 ± 5	<0·001
3.. ..	1	10	53 ± 2	98 ± 2	<0·001

The calcium content of a hand of each of the patients was measured by a neutron activation technique (Catto *et al.*, 1973 a). The neutrons, provided by a 25-Ci source of ^{241}americium and ^{9}beryllium, produced the radioisotope ^{49}Ca from the ^{48}Ca present in the bones of the hand; by detecting and quantifying the gamma-radiation from the induced ^{49}Ca an assessment of the calcium content of the hands was made. Nine activation analyses were performed on each patient during the period of 18 months before treatment with 1α-OHCC began; a further three studies were made at intervals of one month after the start of therapy.

A daily dose of 2 μg 1α-OHCC dissolved in arachis oil was given by mouth to each patient. After three weeks the treatment in case 3 was discontinued for two weeks and then restarted at a dose of 1 μg daily.

Student's *t* test was used to assess the significance of the increase in calcium absorption (tables I and II) and of the alteration in the rate of calcium loss after treatment (table III).

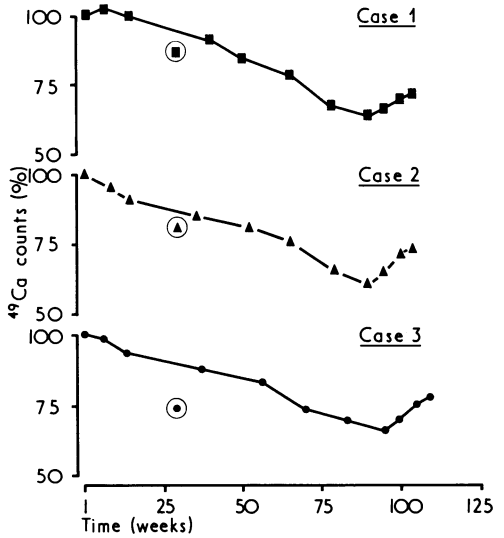
TABLE III—*Rate of Change in Calcium Content (%) per Week ± S.E.*

Case No.	Before 1α-OHCC	After 1α-OHCC	P
1	− 0·44 ± 0·03	+ 0·44 ± 0·05	<0·001
2	− 0·49 ± 0·02	+ 0·77 ± 0·15	<0·001
3	− 0·39 ± 0·02	+ 0·80 ± 0·10	<0·001

Results

After an oral dose of 1α-OHCC 2 μg daily calcium absorption increased significantly in all three patients (table I). These increases persisted during the period studied (table II).

The results of the activation analyses, expressed as the percentage changes from the original ^{49}Ca counts, showed a significant alteration in the rate of change in the calcium content of each hand (table III), which had been falling but increased in all three patients after treatment was started (see fig.). The



Results of activation studies in cases 1, 2, and 3. Arrows indicate start of treatment with 1α-OHCC.

results marked with a circle in the fig. are inaccurate; the fault was due to a leak in the standard used to calibrate the equipment. Though these values were not used when calculating the data shown in table III their inclusion does not alter the significance of the results.

Serial measurements of the plasma concentrations of both calcium and phosphorus in cases 1 and 2 showed little change after treatment with 1α-OHCC. Hypercalcaemia, with a plasma calcium concentration of 3·5 mmol/l., was noted in case 3 14 days after the start of treatment; when the drug was withdrawn plasma calcium concentrations returned to normal values within four days.

Discussion

Though neutron activation analysis was first introduced into clinical practice in 1964 to study sodium metabolism (Anderson *et al.*, 1964) it has been used principally to measure total body calcium (Nelp *et al.*, 1970). The results obtained from total body studies have been reliable (Fremlin, 1972) but the technique has not been widely accepted both because of the complex equipment required and because the whole body radiation dose to the patient restricts the number of measurements to one or two a year. Moreover, the interpretation of the results in patients with renal osteodystrophy has been complicated by the presence of ectopic calcification (Cohn *et al.*, 1972).

The coefficient of variation for the partial body activation technique used in the present study was assessed by repeated measurements of anatomical specimens and for clinical studies is between 4% and 5% (Catto *et al.*, 1973 a). The technique may be a more sensitive indicator of the rate of progression of or improvement in renal bone disease than either skeletal radiography or photon absorption by a radius (Catto *et al.*, 1973 b). Thus it was thought that this method of activation analysis might be of value in assessing the efficacy of 1α-OHCC in promoting the remineralization of diseased bone.

The three patients in this study were selected from a group of patients on maintenance haemodialysis currently being investigated by activation analysis; selection was based on both the histological features of osteomalacia observed in the bone biopsy samples and the rapid rate of skeletal demineralization quantified by the activation technique during the 18 months before treatment started (see fig.). Treatment with 1α-OHCC has now been evaluated for three months; the reversal of the demineralizing process in all three patients studied is a significant result (table III).

The patients, who all received oral calcium supplements, ingested only relatively small quantities of calcium in their usual diets. This has been noted previously in patients with chronic renal failure (Coburn *et al.*, 1973). Brickman *et al.* (1972) reported that 2·5 μg synthetic 1,25-dihydroxycholecalciferol given parenterally to four patients with renal insufficiency increased calcium absorption from the gastrointestinal tract. Similar results were obtained when 1α-OHCC was administered intravenously in a daily dose of 10 to 30 μg (Chalmers *et al.*, 1973) and by mouth in a dose of 25 μg a day (Peacock *et al.*, 1974). We have shown that 1α-OHCC in a dose of only 1 to 2 μg daily is effective in promoting both calcium absorption from the gastrointestinal tract and deposition of calcium in bone.

In case 3, in which the largest increase in calcium absorption on treatment with 1α-OHCC was recorded, symptomatic hypercalcaemia developed. The rapid reduction in plasma calcium concentration to normal levels when therapy was temporarily stopped is of clinical importance as it may indicate that the toxic effects of inadvertent overdosage are of short duration. If confirmed this would represent a substantial advantage over conventional vitamin D therapy.

Neutron activation analysis is the only non-destructive method which measures specifically calcium in vivo. Assessed by this technique 1α-OHCC administered by mouth in a dose of 1 to 2 μg daily produced an increase in the calcium content of bone in three patients on maintenance haemodialysis. This suggests that 1α-OHCC may be an effective treatment for the metabolic bone disease associated with chronic renal failure.

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Prostaglandin E_2 Tablets Compared with Intravenous Oxytocin in Induction of Labour

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Summary

Stimulation of uterine activity after amniotomy has been carried out with prostaglandin E_2 (PGE_2) tablets in two dosage regimens and with intravenous oxytocin. Oxytocin stimulation was the most successful. The difference in success rate was most marked in nulliparous patients and those with a low Bishop score.

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Introduction

The active management of labour with the use of oxytocics to shorten the first stage is rapidly becoming an accepted obstetric practice (Studd, 1973). Prostaglandins E_2 and $F_2\alpha$ have been used as an alternative to oxytocin by the intravenous and, recently, oral routes (Craft, 1972; Kelly *et al.*, 1973). Oral agents are easier to administer than intravenous preparations, do not require pump equipment, and allow the midwife more time for nursing and for monitoring both mother and fetus.

With the introduction of a stable tablet preparation of prostaglandin E_2 (PGE_2; Prostin E_2 dinoprostone) a prospective study was designed to determine its place in the active management of labour.

Materials and Methods

All patients undergoing induction of labour who consented