[8] Saunders L, Natunen T. A four parameter model for oral drug absorption. *J Pharm Pharmacol* 1976;**28**:572-9.
[9] Evans GH, Shand DG. Disposition of propranolol. V. Drug accumulation and steady-state concentrations during chronic oral administration in man. *Clin Pharmacol Ther* 1973;**14**:487-93.
[10] Castleden CM, George CF, Short MD. Contribution of individual differences in gastric emptying to variability in plasma propranolol concentrations. *Br J Clin Pharmacol* 1978;**5**:121-2.
[11] Vestal RE, Wood AJJ, Branch RA, Shand DG, Wilkinson GR. Effects of age and cigarette smoking on propranolol disposition. *Clin Pharmacol Ther* 1979;**26**:8-15.
[12] Wood AJJ, Kornhauser DM, Wilkinson GR, Shand DG, Branch RA. The influence of cirrhosis on steady-state blood concentrations of unbound propranolol after oral administration. *Clin Pharmacokinet* 1978;**3**:478-87.
[13] Lowenthal DT, Briggs WA, Gibson TP, Nelson H, Cirksena WJ. Pharmacokinetics of oral propranolol in chronic renal disease. *Clin Pharmacol Ther* 1974;**16**:761-9.
[14] Feely J, Stevenson IH. The effect of age and hyperthyroidism on plasma propranolol steady state concentration. *Br J Clin Pharmacol* 1978;**6**:446P.
[15] Cotham RH, Shand DG. Spuriously low plasma propranolol concentrations resulting from blood collection methods. *Clin Pharmacol Ther* 1975;**18**:535-8.
[16] Wood M, Shand DG, Wood AJJ. Altered drug binding due to the use of indwelling heparinized cannulas (heparin lock) for sampling. *Clin Pharmacol Ther* 1979;**25**:103-7.

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Double-blind trial of oral 1,25-dihydroxy vitamin D_3 versus placebo in asymptomatic hyperparathyroidism in patients receiving maintenance haemodialysis

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Abstract

Fifty-seven patients who had been receiving maintenance haemodialysis for a mean of 4·6 years were given 0·25-0·5 μg oral 1,25-dihydroxy (1,25-$(OH)_2$) vitamin D_3 or a placebo in a double-blind manner for one to two years. In patients with normal radiographs (mean plasma parathyroid hormone concentration 205 μlEq/ml) 1,25-$(OH)_2$ vitamin D_3 prevented the development of the radiological appearances of hyperparathyroidism. In patients with abnormal radiographs (mean plasma parathyroid concentration 709 μlEq/ml) 1,25-$(OH)_2$ vitamin D_3 arrested or reversed the radiological changes of hyperparathyroidism. Nevertheless, the response was slow and the concentration of the hormone remained considerably raised (mean 445 μlEq/ml).

It is concluded from these results that giving 1,25-$(OH)_2$ vitamin D_3 to patients receiving maintenance haemodialysis who have normal hand radiographs or minimal erosions is beneficial. In patients with more advanced hyperparathyroidism parathyroidectomy should be considered unless there is a rapid response.

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Introduction

By the time patients have been receiving dialysis for five years 15% have disabling bone disease,[1] much of which is due to hyperparathyroidism. At Charing Cross Hospital symptomatic bone disease is uncommon, but in 1976, before the introduction of 1,25-dihydroxy (1,25-$(OH)_2$) vitamin D_3, 16 out of 33 patients who had been receiving dialysis for four years or more showed radiological subperiosteal erosions in the fingers and six had undergone parathyroidectomy. Up to this time oral administration of calcium salts, control of dialysate calcium concentration, and control of plasma phosphate concentration by dietary means or administration of aluminium hydroxide had been used to try to prevent and reverse hyperparathyroidism.

After the introduction of 1,25-$(OH)_2$ vitamin D_3 several favourable reports appeared based on short-term studies.[2-4] We report the results of a controlled clinical trial comparing the effect of administering for one to two years small doses of oral 1,25-$(OH)_2$ vitamin D_3 or an identical placebo capsule to patients receiving dialysis.

Methods

PATIENTS AND DESIGN OF STUDY

The study was started in April 1977, when 127 patients were receiving maintenance haemodialysis. Of these, 106 were receiving home dialysis; 64 entered the trial. The patients were dialysed for 10 hours twice a week using a single-pass system with Kiil dialysers and Cuprophan membranes (PT150). Patients who had plasma calcium concentrations of over 3 mmol/l (12 mg/100 ml) or symptomatic hyperparathyroidism, had already received 1,25-$(OH)_2$ vitamin D_3 or 1α-OH vitamin D_3, or had had a parathyroidectomy were excluded from the trial. Similarly, because of the tendency of patients to show transient improvement in radiological hyperparathyroidism when they first receive maintenance haemodialysis[5] patients were not entered into the trial until they had been receiving dialysis for at least a year. Then one of us (APR), who had no contact with the patients, allocated them into two groups to receive either 0·5 μg 1,25-$(OH)_2$ vitamin D_3 or an identical placebo capsule.

The patients were seen every month for three months and then at three-monthly intervals. At each visit (two to eight hours before

dialysis) they were asked to report any symptoms. A squatting test, in which the patient was asked to squat and rise unaided, was performed; plasma calcium, phosphate, and 25-OH vitamin D concentrations and alkaline phosphatase activity were measured. If the plasma calcium concentration rose to over 3 mmol/l (12 mg/100 ml) the capsules were stopped; when the concentration had returned to normal capsules of a different colour containing, in the treatment group, 0·25 μg 1,25-$(OH)_2$ vitamin D_3 were started. An aluminium hydroxide preparation was given as necessary to keep the plasma phosphate concentration below 2 mmol/l (6 mg/100 ml). Calcium supplements were not given at any time during the trial. The height and span of the patients and the plasma concentration of parathyroid hormone were measured every six months.

Non-screen radiographs of the hands were obtained every six months. All the films, including the ones taken at the start of the trial, were examined at the end of the trial and graded from 0 to 4 by LBT, who had no clinical knowledge of the patients. In this assessment the dates on each patient's films were temporarily covered up to ensure objectivity. The radiographic grades were defined as follows: 0 = normal; 1 = mild erosions, affecting only the radial aspect of one or two phalanges or distal tuft, or both; 2 = more pronounced phalangeal erosions, often of both the radial and ulnar aspects; 3 = pronounced erosions often of several phalanges and metacarpals; subchondral erosions sometimes present at joints; and 4 = extensive subperiosteal and subchondral erosions including erosions of the carpal and forearm bones. Borderline films were assigned half grades—that is, ½, 1½, 2½, 3½; those initially scored as ½ (questionable early erosions) were regarded as normal.

Of the 64 patients who entered the trial, 57 were still in it at one year (30 (19 men, 11 women) in the placebo group and 27 (18 men, nine women) in the treatment group). The mean age was 49·2 ± 11·2 years (placebo group 48·3 ± 12·1; treatment group 50·1 ± 10·3). The mean duration of dialysis before the start of the trial was 4·6 ± 2·6 years (placebo group 4·0 ± 2·3; treatment group 5·3 ± 2·8). During the first year seven patients were removed from the trial; four were in the treatment group (two died and two received transplants), and three in the placebo group (one died and two underwent parathyroidectomy). At the end of the trial in March 1980, 32 of the 57 patients (15 in the placebo group and 17 in the treatment group) had been in the trial for two years. Nineteen had been in the trial for between one and two years so could be assessed at one year but not at two years. The remaining six patients had been removed from the trial between one and two years; two had been in the treatment group (one had died and one had received a transplant) and four in the placebo group (two had died, one had received a transplant, and one had undergone parathyroidectomy).

PLASMA ESTIMATIONS

Total plasma calcium and phosphate concentrations and alkaline phosphatase activity were measured by an autoanalyser. Immunoreactive parathyroid hormone concentration was measured by a double antibody technique,[6] using antibody specific for the carboxy-terminal provided by Dr E Slatopolsky, Washington University School of Medicine, St Louis, Missouri. Plasma 25-OH vitamin D concentration was measured by a competitive protein-binding radioassay.[7]

ASSESSMENT OF RESULTS AT ONE AND TWO YEARS

Changes were regarded as important as follows: *Radiographs*—A change of one grade or more. *Plasma concentration of parathyroid hormone*—A change of more than two coefficients of variation of the assay (that is, 30%). *Plasma calcium concentration*—A rise to 3 mmol/l or from subnormal to normal values or a consistent rise of 20% within or above the normal range; similarly, a fall from normal to subnormal values or a consistent fall of 20%. *Plasma phosphate concentration*—A consistent change of 25%. *Plasma alkaline phosphatase activity*—A consistent change of 25% unless the initial value was below 5 KA units/100 ml.

STATISTICAL METHODS

The significance of differences in proportions was assessed by Fisher's exact test for 2 × 2 contingency tables and by χ^2 for 3 × 2 contingency tables. Wilcoxon's signed ranks and sum of ranks tests; were used to assess the significance of mean differences and differences of the means respectively. The degree of correlation between two variables was determined by the Spearman rank correlation coefficient (r_s).

Results

RADIOGRAPHS (fig 1)

Incidence of deterioration in the 57 patients—At one year radiological deterioration had occurred in 16 of the 30 patients receiving placebo but in only one of the 27 patients receiving 1,25-$(OH)_2$ vitamin D_3. At two years radiological deterioration had occurred in 12 of the 15 patients given placebo and in three of the 17 given 1,25-$(OH)_2$ vitamin D_3 ($p < 0·01$).

Incidence of improvement in the 36 patients with abnormal radiographs—Of the 20 patients with abnormal radiographs initially who were given placebo for one year, not one improved radiologically, whereas five of the 16 given 1,25-$(OH)_2$ vitamin D_3 for one year improved. At two years none of the 11 patients given placebo had improved. In contrast, five of the 11 patients given 1,25-$(OH)_2$ vitamin D_3 for two years had improved. This tendency of 1,25-$(OH)_2$ vitamin D_3 to reverse established radiological abnormalities was significant at both one and two years ($p < 0·05$). Only four of the 16 patients given 1,25-$(OH)_2$ vitamin D_3, however, showed complete radiological healing.

Incidence of deterioration in the 21 patients with normal radiographs—Of the 10 patients receiving placebo whose initial radiographs were normal, two had developed radiological abnormalities by the end of one year; in contrast, in all 11 patients receiving 1,25-$(OH)_2$ vitamin D_3 the radiographs remained normal. These observations, while not significant, show that 1,25-$(OH)_2$ vitamin D_3 tends to prevent the development of radiological erosions in patients with normal radiographs.

PLASMA PARATHYROID HORMONE (tables I and II)

Initial plasma concentration—The mean plasma parathyroid hormone concentration before the trial in the 55 patients in whom it was measured was 535 ± 447 μlEq/ml (normal 2-8 μlEq/ml). In the 35 patients with abnormal hand radiographs the mean was 706 ± 510 μlEq/ml; in the 20 patients with normal radiographs it was 238 ± 189 μlEq/ml ($p < 0·002$). Overall, the concentration was significantly

TABLE I—*Mean plasma concentrations before start of trial*

	All patients	Patients with abnormal radiographs	Patients with normal radiographs	Abnormal radiographs: 1,25-$(OH)_2$ vitamin D_3	Abnormal radiographs: Placebo	Normal radiographs: 1,25-$(OH)_2$ vitamin D_3	Normal radiographs: Placebo
No of patients	57	36	21	16	20	11	10
Parathyroid hormone (μlEq/ml)	535 ± 477 (n = 55)	706 ± 510 (n = 35)	238 ± 189 (n = 20)	765 ± 614 (n = 15)	662 ± 427 (n = 20)	205 ± 197 (n = 11)	277 ± 180 (n = 9)
		$p < 0·02$		NS		NS	
Calcium (mmol/l)	2·51 ± 0·28	2·52 ± 0·31	2·41 ± 0·24	2·45 ± 0·31	2·59 ± 0·21	2·54 ± 0·26	2·44 ± 0·23
		NS		NS		NS	
Phosphate (mmol/l)	1·76 ± 0·48	1·77 ± 0·48	1·75 ± 0·51	1·63 ± 0·40	1·88 ± 0·51	1·88 ± 0·56	1·61 ± 0·42
		NS		NS		NS	
Alkaline phosphatase (KA units/100 ml)	13·3 ± 9·5	15·3 ± 11·2	9·8 ± 3·6	20·2 ± 15·2	11·4 ± 3·4	9·1 ± 4·3	10·7 ± 2·5
		$p < 0·02$		$p < 0·01$		NS	

Conversion: SI to traditional units—Calcium: 1 mmol/l ≈ 4 mg/100 ml. Phosphate: 1 mmol/l ≈ 3·1 mg/100 ml.

TABLE II—*Distribution of patients showing changes in plasma concentrations at one and two years*

		Total No of patients	Parathyroid hormone*				Calcium				Phosphate				Alkaline phosphatase			
			Rise	No change	Fall	Rise v no rise	Fall v no fall	Rise†	No change	Fall	Rise v no rise	Fall v no fall	Rise	No change	Fall	Rise v no rise	Fall v no fall
All patients (n=57)																	
1 year	Placebo	30	10	13	4	NS	NS	0	29	1	p<0·01	NS	0	26	4	p=0·05	NS	7	21	2	NS	p<0·01
	1,25-(OH)$_2$D$_3$	27	4	10	10			17 (13)	10	0			5	19	3			1	14	12		
2 years	Placebo	15	6	6	3	p=0·05	NS	0	14	1	p<0·01	NS	1	12	2	—	NS	7	8	0	NS	NS
	1,25-(OH)$_2$D$_3$	17	1	7	8			13 (3)	4	0			0	14	3			2	5	10		
Patients with abnormal radiographs (n=36)																	
1 year	Placebo	20	8	9	2	NS	p<0·05	0	19	1	p<0·01	NS	0	16	4	NS	NS	6	14	0	p<0·05	p<0·05
	1,25-(OH)$_2$D$_3$	16	3	4	6			8 (5)	8	0			3	12	1			0	7	9		
2 years	Placebo	11	5	5	1	NS	NS	0	10	1	p<0·01	NS	1	8	2	—	NS	5	6	0	NS	p<0·01
	1,25-(OH)$_2$D$_3$	11	1	5	4			8 (3)	3	0			0	9	2			1	3	7		
Patients with normal radiographs (n=21)																	
1 year	Placebo	10	2	4	2	NS	NS	0	10	0	p<0·01	—	0	10	0	NS	NS	1	7	2	NS	NS
	1,25-(OH)$_2$D$_3$	11	1	6	4			9 (8)	2	0			2	7	2			1	7	3		
2 years	Placebo	4	1	1	2	NS	NS	0	4	0	NS	—	0	4	0	—	NS	2	2	0	NS	NS
	1,25-(OH)$_2$D$_3$	6	0	2	4			5	1	0			0	5	1			1	2	3		

*Serial estimations of parathyroid hormone concentrations were done in 51 of the 57 patients at one year and 31 at two years.
†Figures in parentheses refer to the numbers of patients in whom the dose of 1,25-(OH)$_2$ vitamin D$_3$ was halved because the plasma calcium concentration rose to 3 mmol/l (12 mg/100 ml).

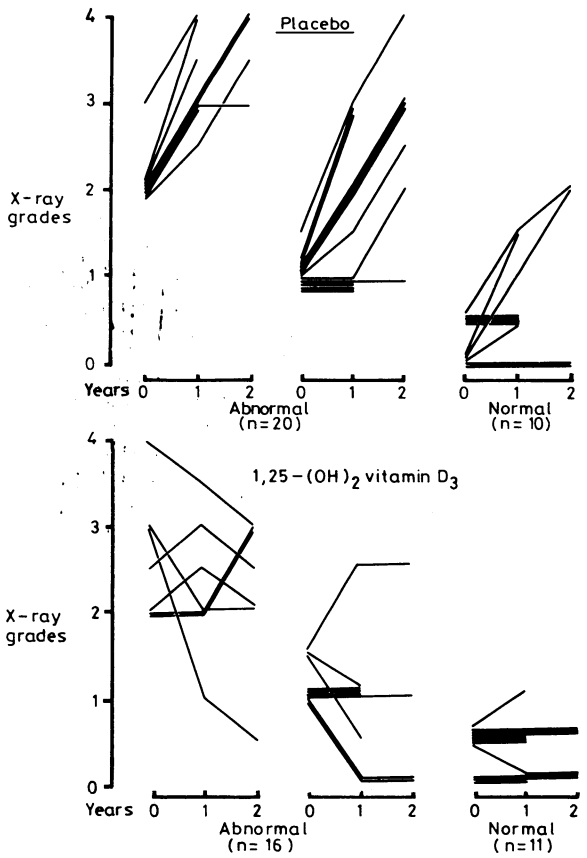

FIG 1—Radiographic grades initially and at one and two years.

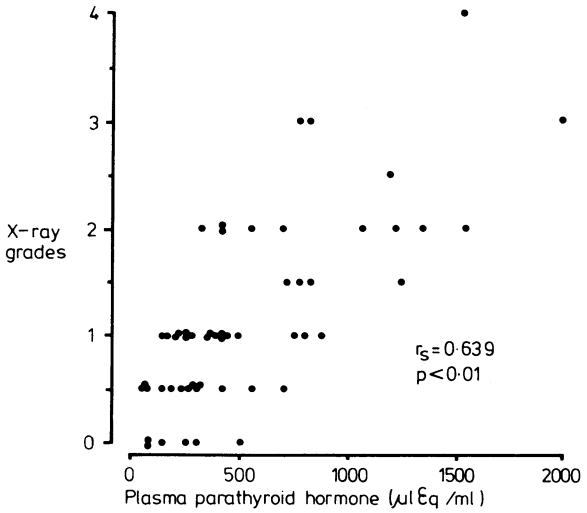

FIG 2—Correlation between radiographic grades and plasma concentrations of parathyroid hormone at start of trial.

related to the extent of radiographic evidence of hyperparathyroidism ($r_s = 0{\cdot}639$, $p < 0{\cdot}01$) in the hands (fig 2).

Changes in concentration during the trial—Serial estimations were carried out in 51 patients. At the start of the trial the mean plasma concentration of parathyroid hormone was 543 ± 866 μlEq/ml in the 27 patients given placebo and 528 ± 673 μlEq/ml in the 24 patients given 1,25-(OH)$_2$ vitamin D$_3$ ($p > 0{\cdot}05$). At one year the mean concentration had risen to 705 ± 571 μlEq/ml in the patients receiving placebo ($p > 0{\cdot}05$) and fallen to 301 ± 326 μlEq/ml in the patients receiving 1,25-(OH)$_2$ vitamin D$_3$ ($p = 0{\cdot}05$). Although the proportion of patients who showed a fall in plasma parathyroid hormone concentration was

greater in those given 1,25-$(OH)_2$ vitamin D_3 than in those given placebo, the difference was not significant at one and two years. A greater proportion of patients given placebo than 1,25-$(OH)_2$ vitamin D_3 showed a rise in plasma concentration; this difference was not significant at one year but was probably significant at two years ($p = 0.05$).

Changes in the 32 patients with abnormal radiographs—Initially the mean plasma parathyroid hormone concentration was 667 ± 438 μlEq/ml in the 19 patients receiving placebo and 709 ± 621 μlEq/ml in the 13 patients receiving 1,25-$(OH)_2$ vitamin D_3 ($p > 0.05$). At one year the mean concentration had risen to 865 ± 590 μlEq/ml in the patients given placebo and fallen to 445 ± 384 μlEq/ml in the patients given 1,25-$(OH)_2$ vitamin D_3, but these differences were not significant. On the other hand, at one year the proportion of patients in whom the concentration had fallen was significantly greater in the group receiving 1,25-$(OH)_2$ vitamin D_3 ($p < 0.05$). Nevertheless, the concentration had risen in three patients receiving 1,25-$(OH)_2$ vitamin D_3 at one year.

Changes in the 19 patients with normal radiographs—The initial mean concentration in patients receiving placebo was 273 ± 192 μlEq/ml and in those receiving 1,25-$(OH)_2$ vitamin D_3 205 ± 197 μlEq/ml ($p > 0.05$). At one year the mean concentration had risen to 349 ± 331 μlEq/ml in the patients receiving placebo and fallen to 131 ± 94 μlEq/ml in the patients receiving 1,25-$(OH)_2$ vitamin D_3 (both changes not significant). There were no significant differences between the proportions of patients receiving placebo and 1,25-$(OH)_2$ vitamin D_3 who showed a rise or a fall in concentration at one and two years.

PLASMA CALCIUM (tables I and II)

Initial mean plasma concentration of calcium in the 57 patients was $2.51 \pm$ SD 0.28 mmol/l (10 ± 1 mg/100 ml). There was no correlation between plasma calcium and plasma parathyroid hormone concentrations ($r_s = 0.0204$, $p > 0.05$). There was no difference in the initial mean plasma calcium concentration between the patients with normal and abnormal radiographs ($p > 0.5$).

Changes during the trial in the 57 patients—The plasma calcium concentration had risen in 17 of the 27 patients receiving 1,25-$(OH)_2$ vitamin D_3 at the end of the first year and in 13 of the 17 patients still receiving 1,25-$(OH)_2$ vitamin D_3 during the second year. The dose was halved in 16 of the original 27 patients because the calcium concentration had risen above 3 mmol/l (12 mg/100 ml). The concentration did not rise in any of the patients who received placebo ($p < 0.01$). None of the 57 patients showed a consistent change in plasma albumin concentration.

Changes in patients with abnormal radiographs—In eight of the 16 patients receiving 1,25-$(OH)_2$ vitamin D_3 calcium concentration had risen by one year; in five of these the dose was halved. Of the 11 reaching two years, eight had experienced a rise in plasma calcium concentration at some time. In three of these eight the dose was halved during the second year because the concentration exceeded 3 mmol/l.

Changes in patients with normal radiographs—In nine of the 11 patients receiving 1,25-$(OH)_2$ vitamin D_3 calcium concentration had risen by one year; in eight of the nine the dose was halved because the concentration exceeded 3 mmol/l. During the second year the concentration remained below 3 mmol/l in all patients.

PLASMA PHOSPHATE (tables I and II)

The mean plasma phosphate concentration in the 57 patients was initially 1.76 ± 0.48 mmol/l (5.5 ± 1.5 mg/100 ml). At one year a greater proportion of patients receiving 1,25-$(OH)_2$ vitamin D_3 had shown a rise in plasma phosphate concentration ($p = 0.05$). Within the groups with normal and abnormal radiographs there were no significant differences between the proportions of patients receiving placebo and treatment who showed a rise or fall in plasma phosphate concentration at one and two years.

ALUMINIUM HYDROXIDE ADMINISTRATION

At the start of the trial 18 patients (12 receiving placebo and six treatment) were taking an aluminium hydroxide preparation (Alucap Riker, 475 mg/capsule). At one year 16 of the 30 patients in the placebo group and 14 of the 27 in the treatment group were receiving aluminium hydroxide.

PLASMA CALCIUM × PLASMA PHOSPHATE PRODUCT

Initially the product of the plasma calcium and plasma phosphate concentrations was intermittently raised (over 5·5) in 10 of the 36 patients with abnormal radiographs (six of the 30 receiving placebo and four of the 16 receiving treatment). In no patient was the product persistently raised. At one year the product had risen in one patient receiving treatment and fallen in four patients (two receiving placebo and two treatment). There was no significant difference between the two groups at one or two years. Initially seven of the 21 patients with normal radiographs (two of the 10 receiving placebo and five of the 11 receiving treatment) had intermittently high products. By one year the only change had been a fall in a patient receiving 1,25-$(OH)_2$ vitamin D_3. There was no appreciable difference between any of the groups.

PLASMA ALKALINE PHOSPHATASE (tables I and II)

Initial plasma activity—Initially 32 of the 57 patients had a plasma alkaline phosphatase activity greater than 10 KA units/100 ml. Seven of the patients with raised and two of the patients with normal activity had a high plasma alanine transferase activity. Mean plasma alkaline phosphatase activity was significantly higher in patients with abnormal radiographs ($p < 0.02$). In this group the activity was higher in patients about to receive 1,25-$(OH)_2$ vitamin D_3 than in those about to receive placebo ($p < 0.01$), but this difference was not significant when patients with abnormal liver enzyme activities were excluded ($p > 0.05$).

Changes during the trial in the 57 patients—At one year a higher proportion of patients receiving 1,25-$(OH)_2$ vitamin D_3 showed a fall in plasma alkaline phosphatase activity ($p < 0.01$). At two years this trend was less pronounced. The proportions of patients showing a rise was not significant in the two groups at one and two years.

Changes in the 36 patients with abnormal radiographs—At one year the proportion of patients in whom plasma alkaline phosphatase activity had risen was significantly greater in the placebo group ($p < 0.05$). The proportion of patients in whom activity had fallen was significantly greater in the group receiving 1,25-$(OH)_2$ vitamin D_3 at one ($p < 0.01$) and two years ($p < 0.05$).

Changes in the 21 patients with normal radiographs—There were no significant differences in activity between the patients receiving placebo and treatment.

PLASMA 25-OH VITAMIN D CONCENTRATIONS

Initial plasma 25-OH vitamin D concentrations were within the normal range in all 57 patients. Minor changes within the normal range occurred during the trial, which could be attributed to seasonal variation. There were no significant differences between patients receiving placebo and those receiving 1,25-$(OH)_2$ vitamin D_3.

SYMPTOMS AND CLINICAL EVALUATION

Two patients lost over 2 cm in height during the first year; two further patients lost more than 2 cm during the second year. All four patients were receiving placebo; their initial radiographs showed evidence of hyperparathyroidism, which became worse during the trial.

As already mentioned, only asymptomatic patients were included in the trial. No consistent symptoms developed during the trial in any of the groups of patients. There was an improvement in two out of four patients who had initially had an abnormal squatting test, and none developed an abnormal test during the trial.

Discussion

Around 65-70% of patients about to start maintenance haemodialysis have radiological evidence of hyperparathyroidism.[8] Quantitative bone histology, however, shows that this complication is present in 90% of patients.[8 9] The study described here of the effect of 1,25-$(OH)_2$ vitamin D_3 on the hyperparathyroidism of patients receiving maintenance haemodialysis is the first controlled trial performed under double-blind conditions in which observations have been made for over

three months.[10 11] The patients were divided into those with normal and those with abnormal hand radiographs, and the effect of 1,25-$(OH)_2$ vitamin D_3 was, to a large extent, based on detailed examination of serial radiographs, a technique that is non-invasive, convenient, and generally available. While measurement of plasma concentrations of parathyroid hormone and quantitative bone histology may be more precise than radiographs in assessing the progress of hyperparathyroidism,[12-18] these methods are less widely available.

Clearly, when radiographs are used to monitor progress it is important that the radiological assessment is quantitative and that the films are scored by a radiologist not in day-to-day contact with the trial and unaware of the chronological sequence of each individual's films.[19] It is also important that the criteria used to quantitate the radiological appearances should be clearly defined.

Our results show that administering 1,25-$(OH)_2$ vitamin D_3, 0·25-0·50 μg/day, over one to two years either arrests or improves the radiological features of hyperparathyroidism, although the radiographs become completely normal in only four patients. This observation is in line with the finding of others that 1,25-$(OH)_2$ vitamin D_3 can arrest progressive hyperparathyroidism[3 4 15 20] but rarely induces complete healing.[14] The results also suggest that in patients with normal hand radiographs administration of 1,25-$(OH)_2$ vitamin D_3 can prevent the development of subperiosteal erosions. In this study the rigid constraints imposed by a double-blind controlled trial may have slightly masked the beneficial effect of 1,25-$(OH)_2$ vitamin D_3. Two patients who had to undergo parathyroidectomy before they had reached one year, and therefore were not included in the assessment of the results, subsequently proved to have been in the placebo group. On the other hand, we have evidence that two patients in the treatment group who completed two years and therefore were included in the assessment did not take the vitamin regularly.

The plasma concentration of parathyroid hormone was significantly related to the severity of the radiographic changes.[21] During the trial there was an insignificant rise in plasma parathyroid concentration in those who were receiving placebo whereas there was a small but significant fall in the concentration in patients taking 1,25-$(OH)_2$ vitamin D_3. As has been reported by others,[14 15 20] however, the plasma concentration remained high even in patients whose hand radiographs improved. The apparent inability of 1,25-$(OH)_2$ vitamin D_3 significantly to lower plasma concentrations of parathyroid hormone and the occasional discrepancy between the change in radiological appearances and changes in these concentrations may be due to the propensity of the C-terminal assay to recognise inactive fragments.[22] Nevertheless, the initial significant correlation between the plasma concentration of parathyroid hormone and the radiological evidence of hyperparathyroidism suggests that the concentration as measured by the C-terminal assay parallels that of the active hormone.

There was no correlation between pretreatment plasma parathyroid hormone and calcium concentrations. During the trial a fall in plasma parathyroid hormone concentration was usually accompanied by a rise in total plasma calcium concentration, but in a few patients a fall in plasma parathyroid hormone concentration and radiographic improvement preceded a significant rise in plasma calcium concentration.[15 17] Without measurement of plasma ionised calcium[18] it is impossible to say whether this fall in parathyroid hormone concentration in these patients was a direct effect of 1,25-$(OH)_2$ vitamin D_3 on the parathyroid glands.[23]

The dose of 1,25-$(OH)_2$ vitamin D_3 was fairly low. Nevertheless, it had to be reduced in 16 of the 27 patients to avoid persistent hypercalcaemia. The incidence of hypercalcaemia was 50% in patients with abnormal radiographs and 73% in the others, findings similar to those of Winkler *et al.*[24] Radiographic improvement was usually accompanied by a rise in plasma calcium concentration, but in three patients in whom the hypercalcaemia occurred during the first six months the radiographs did not change at that time or, subsequently, when the dose of 1,25-$(OH)_2$ vitamin D_3 was reduced. In these patients the gut appears to have been unduly sensitive to 1,25-$(OH)_2$ vitamin D_3. The subsequent lack of radiological improvement may have been due to an insufficiently sustained rise in plasma calcium concentration, or, alternatively, the plasma concentration of 1,25-$(OH)_2$ vitamin D_3 at the smaller dose may not have been high enough to suppress the parathyroid glands.

Treatment with 1,25-$(OH)_2$ vitamin D_3 produced a small rise in plasma phosphate concentration, which was probably attenuated by our traditional insistence on maintaining this concentration below 2 mmol/l (6 mg/100 ml)[25 26] by giving aluminium hydroxide. This rise supports the claim that 1,25-$(OH)_2$ vitamin D_3 causes a rise in plasma phosphate concentration in patients receiving maintenance haemodialysis,[17 18 20 27] although others do not agree.[10 14] In contrast to Binswanger *et al*[18] we found that it was not particularly difficult to control plasma phosphate concentration in patients with normal radiographs, although in four the product of the plasma calcium and plasma phosphate concentrations was intermittently raised. Inspection of the available *x*-ray films did not show any difference in the incidence of soft-tissue calcification between the treatment and placebo groups. We would suggest that if plasma calcium and phosphate concentrations are repeatedly estimated and the dose of aluminium hydroxide regularly adjusted 1,25-$(OH)_2$ vitamin D_3 may be administered even to patients with no radiographic evidence of hyperparathyroidism (a group in whom treatment with vitamin D is associated with a high incidence of hypercalcaemia and hyperphosphataemia). We would agree with Baker *et al*[28] that, to avoid hypercalcaemia and hyperphosphataemia in patients receiving maintenance haemodialysis with normal hand radiographs, the initial dose of 1,25-$(OH)_2$ vitamin D_3 should probably be 0·25 μg/day.

Plasma activity of alkaline phosphatase was higher in the patients with abnormal radiographs than in those with normal radiographs; in a third of the patients it was normal. In patients receiving 1,25-$(OH)_2$ vitamin D_3 the activity fell significantly. In some patients the interpretation of the changes in total plasma alkaline phosphatase activity was made difficult by the presence of hepatitis.

In conclusion, our results suggest that in patients who have no radiological evidence of hyperparathyroidism or in whom such changes are relatively mild administration of 1,25-$(OH)_2$ vitamin D_3 will prevent the development of progressive erosions. Hypercalcaemia and hyperphosphataemia are an undoubted risk in such patients. We have found, however, that provided that frequent measurements are made such risks can be avoided. In those in whom the radiological appearances are more pronounced and the plasma concentrations of parathyroid hormone considerably higher the beneficial effects of 1,25-$(OH)_2$ vitamin D_3 are less certain, particularly when the plasma calcium concentration is in the upper-normal range before the start of treatment. Even when 1,25-$(OH)_2$ vitamin D_3 improves the radiological appearances and causes some lowering in plasma parathyroid hormone concentration, the response is slow and the plasma concentration usually remains considerably raised.[14 20] In such patients we would agree with the suggestion that it is probably better to perform parathyroidectomy than to give a prolonged course of 1,25-$(OH)_2$ vitamin D_3,[14] unless the response to 1,25-$(OH)_2$ vitamin D_3 is rapid. We also agree with Kanis *et al*[14] that a short preoperative course of 1,25-$(OH)_2$ vitamin D_3 in such patients is useful in preventing severe postoperative hypocalcaemia.

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References

[1] Brunner FP, Brynger H, Chantler C, *et al.* Combined report on regular dialysis and transplantation in Europe. *Proc Eur Dial Transplant Assoc* 1979;**16**:2-73.

[2] Brickman AS, Coburn JW, Norman AW. Action of 1,25-dihydroxycholecalciferol, a potent kidney-produced metabolite of vitamin D_3 in uremic man. *N Engl J Med* 1972;**287**:891-5.

[3] Brickman AS, Sherrard DJ, Jowsey J, *et al.* 1,25-dihydroxycholecalciferol. Effect on skeletal lesions and plasma parathyroid hormone levels in uremic osteodystrophy. *Arch Intern Med* 1974;**134**:883-8.

[4] Henderson RG, Russell RGG, Ledingham JGG, *et al.* Effects of 1,25-dihydroxycholecalciferol on calcium absorption, muscle weakness and bone disease in chronic renal failure. *Lancet* 1974;i:379-84.

[5] de Wardener HE, Eastwood JB. The management of renal osteodystrophy. *Adv Exp Med Biol* 1977;**81**:533-47.

[6] Conaway HH, Anast CS. Double-antibody radioimmunoassay for parathyroid hormone. *J Lab Clin Med* 1974;**83**:129-38.

[7] Haddad JG, Chyu KJ. Competitive protein-binding radioassay for 25-hydroxycholecalciferol. *J Clin Endocrinol Metab* 1971;**33**:992-5.

[8] Eastwood JB. *Observations on renal osteodystrophy with special reference to the action of vitamin D on bone mineralisation.* MD thesis. London: University of London, 1974:110-6.

[9] Ellis HA, Peart KM. Azotaemic renal osteodystrophy: a quantitative study on iliac bone. *J Clin Pathol* 1973;**26**:83-101.

[10] Berl T, Berns AS, Huffer WE, *et al.* 1,25-dihydroxycholecalciferol effects in chronic dialysis. A double-blind controlled study. *Ann Intern Med* 1978;**88**:774-80.

[11] Maxwell DR, Benjamin DM, Donahay SL, Allen MK, Hamburger RJ, Luft FC. Calcitriol in dialysis patients. *Clin Pharmacol Ther* 1978;**23**:515-9.

[12] Hochman B, Gura V, Boner G, Weiss A, Olah AJ, Rosenfeld J. Long term effects of small doses of 1,25-dihydroxycholecalciferol in dialysis patients. In: Norman AW, Schaefer K, von Herrath D, *et al*, eds. *Vitamin D. Basic research and its clinical application.* Berlin: De Gruyter, 1979:803-6.

[13] Olah AJ, Jahn H, Reutter FW, Konig R, Blumberg A, Colombi A. Histomorphometry of bone changes in renal osteodystrophy after treatment with 1,25-dihydroxycholecalciferol. In: Norman AW, Schaefer K, von Herrath D, *et al*, eds. *Vitamin D. Basic research and its clinical application.* Berlin: De Gruyter, 1979:817-20.

[14] Kanis JA, Cundy T, Earnshaw M, *et al.* Treatment of renal bone disease with 1α-hydroxylated derivatives of vitamin D_3. *Q J Med* 1979;**48**:289-322.

[15] Coburn JW, Brickman AS, Sherrard DJ, Singer FR, Wong EGC, Norman AW. The renal osteodystrophies: clinical features in patients classified by histologic features and their response to treatment with 1,25-dihydroxyvitamin D_3. In: Norman AW, Schaefer K, von Herrath D, *et al*, eds. *Vitamin D. Basic research and its clinical application.* Berlin: De Gruyter, 1979:1217-22.

[16] Sherrard DJ, Coburn JW, Brickman AS, Singer FR, Maloney N. Skeletal response to treatment with 1,25-dihydroxy vitamin D in renal failure. *Contrib Nephrol* 1980;**18**:92-7.

[17] Brickman AS, Coburn JW, Sherrard DJ, Wong EGC, Norman AW, Singer FR. Clinical effects of 1,25-dihydroxy vitamin D_3 in uremic patients with overt osteodystrophy. *Contrib Nephrol* 1980;**18**:29-41.

[18] Binswanger U, Fisher JA, Iselin H, *et al.* 1,25-dihydroxycholecalciferol treatment of clinically asymptomatic renal osteodystrophy. *Mineral and Electrolyte Metabolism* 1979;**2**:103-15.

[19] Guerra LE, Amato JA, Maher JF. Inconsistency in radiographic evaluation of progressive renal osteodystrophy. *Clin Nephrol* 1979;**11**:307-12.

[20] Goldstein DA, Malluche HH, Massry SG. Long term effects of 1,25-$(OH)_2D_3$ on clinical and biochemical derangements of divalent ions in dialysis patients. *Contrib Nephrol* 1980;**18**:42-54.

[21] Goldsmith RS, Furszyfer J, Johnson WJ, Fournier AE, Arnaud CD. Control of secondary hyperparathyroidism during long-term hemodialysis. *Am J Med* 1971;**50**:692-9.

[22] Segre GV, Habener JF, Powell D, Tregear GW, Potts JT Jr. Parathyroid hormone in human plasma. Immunochemical characterization and biological implications. *J Clin Invest* 1972;**51**:3163-72.

[23] Wecksler WR, Henry HL, Norman AW. Studies on the mode of action of calciferol. Subcellular localization of 1,25-dihydroxyvitamin D_3 in chicken parathyroid glands. *Arch Biochem Biophys* 1977;**183**:168-75.

[24] Winkler SN, Brickman AS, Wong EGC, *et al.* Hypercalcemia during treatment of uremic patients with 1,25-$(OH)_2D_3$: analysis of 43 cases. In: Norman AW, Schaefer K, von Herrath D, *et al*, eds. *Vitamin D. Basic research and its clinical application.* Berlin: De Gruyter, 1979:851-2.

[25] Curtis JR, Eastwood JB, Smith EKM, *et al.* Maintenance haemodialysis. *Q J Med* 1969;**38**:49-89.

[26] Parfitt AM, Massry SG, Winfield AC, DePalma JR, Gordon A. Disordered calcium and phosphorus metabolism during maintenance hemodialysis. Correlation of clinical, roentgenographic and biochemical changes. *Am J Med* 1971;**51**:319-30.

[27] Schulz W, Spiegel P, Delling G. Clinical experience in long term treatment with 1,25-DHCC in different histological forms of renal osteopathy. In: Norman AW, Schaefer K, von Herrath D, *et al*, eds. *Vitamin D. Basic research and its clinical application.* Berlin: De Gruyter, 1979:827-30.

[28] Baker LRI, Muir JW, Cattell WR, *et al.* Use of 1,25-$(OH)_2$ vitamin D_3 in prevention of renal osteodystrophy: preliminary observations. *Contrib Nephrol* 1980;**18**:147-51.

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ONE HUNDRED YEARS AGO *A Case of Paracentesis of the Bladder.*—Mr F J B Quinlan, after briefly alluding to the recent melancholy death of Dr Peele, in company with whom he saw the patient, and performed the operation described in his communication, read the notes of a case which had come under his care in St Vincent's Hospital. An elderly man, grey-haired, had for many years suffered from stricture of the urethra, at intervals more or less protracted. A few days before Mr Quinlan saw him, he was again attacked, and on that occasion he purchased a quantity of whiskey, and drank himself free from pain. On recovering consciousness, his agony was excruciating; and, when Mr Quinlan saw him, he was roaring with the pain. The bladder could be felt hard and bulging, like a large water-melon, in the abdomen. The resident medical officer in the hospital had tried to relieve him by every means: baths, stupes, opiates, etc, but without success. The catheter could not be passed beyond the bulb, where a cartilaginous stricture could be felt. Mr Quinlan also tried to pass the catheter, but with no other effect than the production of copious haemorrhage. The case being urgent, and the man's cries for relief undiminished by the previous treatment, Mr Quinlan passed a large trocar and cannula into the bladder, through the line alba, two inches above the pubes; and this drew off a large quantity of urine, giving immediate relief. There was no suction used in evacuating the contents of the bladder; but, as much as could be pressed out through the cannula having been drawn off, the cannula was removed, the man put to bed with hot jars to his feet, and given one-half grain of acetate of morphia. Next day, the patient expressed himself as quite comfortable, and in a warm bath evacuated his bladder *per vias naturales;* and, in a fortnight, left the hospital—able to micturate, to use his own expression, "as well as in his best days." The stricture in this case was, he considered, a mixed one—partly organic, and partly spasmodic. He had not employed suction in emptying the bladder, as cystitis might be produced by the mucous membrane of the bladder being sucked into the tube. Nor did he approve of the method of leaving the cannula in for any lengthened period; but preferred repeated paracentesis, if necessary.—The Chairman had that day seen a case in which repeated tappings had been resorted to with the most satisfactory result, after a couple of months' treatment.—Mr Ormsby had some time ago tapped a man through the rectum, for spasmodic stricture of the urethra, which resisted all other treatment. The next day, he could with ease pass in a No 5 catheter. This man had been tapped above the pubes, six years before, for a similar attack; but had no attack in the interval, or since the last operation.—Mr A Corley had seen a case some years ago, in company with the chairman, in which an elderly surgeon had endeavoured to tap his own bladder for retention of urine, with unsatisfactory results—insomuch that he (Mr Corley) had to do it also, and the patient subsequently died. Dr Adams had said that the proudest epitaph a surgeon could have on his grave was: "I never tapped a bladder." With this Mr Corley did not agree.—Mr W I Wheeler preferred the suprapubic operation to that *per rectum.* In one case which he had had of contusion stricture, caused by a kick of a horse in the perinaeum, the man was tapped fourteen times, and the urethra gradually dilated up to a No 8 catheter. In another case where there was true traumatic stricture, the man had been tapped twenty times, *per rectum,* before Mr Wheeler saw him; and also afterwards, over the pubes, by Mr Wheeler, previously to performing Cook's operation.—Dr Frazer, Dr Doyle, Dr Cranny, and Mr Warren also took part in the discussion. (*British Medical Journal,* 1881.)