PAPERS AND ORIGINALS

1-alpha-hydroxycholecalciferol for renal osteodystrophy

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Summary

Fourteen patients with renal osteodystrophy were treated for at least one year with 1-alpha-hydroxycholecalciferol (1-alpha-OHD₃) in a dose varying from 1 µg week to 3 µg day. Plasma calcium and inorganic phosphorus concentrations increased significantly. The plasma alkaline phosphatase concentration fell in 11 of the 12 patients in whom it was initially raised and returned to normal in seven. Serum parathyroid hormone concentrations were initially raised in all patients, but they decreased significantly with treatment and became normal in eight patients within one year. The 10 patients with radiological abnormalities showed some improvement. Hypercalcaemia occurred in 11 patients, and necessitated a reduction in the dose of 1-alpha-OHD₃ in some.

1-alpha-OHD₃ was effective in reducing the biochemical and radiological abnormalities of renal osteodystrophy, but it should be used with care, and plasma calcium concentrations should be monitored.

Introduction

Recent advances in the understanding of vitamin D metabolism have led to the use of 1-hydroxylated derivatives of the vitamin in the management of renal osteodystrophy. 1-α-hydroxycholecalciferol (1-α-OHD₃), which is converted to 1,25-dihydroxycholecalciferol (1,25-(OH)₂D₃) in the body,¹ has been used to

treat renal bone disease in several studies.²⁻⁴ Nevertheless, there is little information about its long-term effects on the clinical, biochemical, and radiological abnormalities in patients with osteodystrophy who are undergoing haemodialysis. We therefore studied the effects of this drug in 14 such patients who were treated for at least 12 months.

Patients and methods

Fourteen patients (five female and nine male) aged 16 to 53 years were studied. They had radiological evidence of renal bone disease or a persistently raised plasma alkaline phosphatase concentration in the absence of biochemical evidence of liver disease, or both.

Thirteen of the patients had been undergoing regular haemodialysis for one to 10 years, using a 1-m² Kiil dialyser for 18 to 30 hours a week. One patient with severe chronic renal failure was initially treated by dietary restriction of protein but subsequently required peritoneal dialysis and then regular haemodialysis. The dialysate calcium concentration was 1.6 mmol/l (6.4 mg/100 ml). Dietary calcium and phosphorus were not restricted. The calculated daily intake of calcium was 300 to 1200 mg and that of phosphorus 400 to 1000 mg. Nine patients received aluminium hydroxide throughout the study. The dose remained constant except in two patients whose plasma inorganic phosphorus concentrations changed considerably; the dose of aluminium was reduced in one and increased in the other. Five patients had been treated previously with dihydrotachysterol (AT 10), which was withdrawn at least three months before treatment with 1-α-OHD₃.

Fasting blood samples were taken at least 24 hours after dialysis. Standard methods were used for measuring plasma calcium, inorganic phosphorus, and alkaline phosphatase concentrations. Results for plasma calcium were corrected for specific gravity.⁵ Serum parathyroid hormone was measured in an immunoradiometric assay using anti-serum AS199 (BW211 32).⁶ At the end of the study all samples for each patient were assayed for parathyroid hormone in the same assay at two different dilutions.

Skeletal radiographs were taken before and six and 12 months after starting treatment with 1-α-OHD₃. The radiological assessment was performed by one of us (WH), who attempted to rank the undated films of each patient with respect to the severity of radiological change and to identify those films in which there were no erosive or osteomalacic bone changes. Student's paired *t* test was used for statistical analysis.

In the month before treatment with 1-α-OHD₃ four values of plasma calcium, inorganic phosphorus, and alkaline phosphatase were obtained, and the means of these were used as pretreatment control values for each patient. During the treatment period these concentrations were measured every month. The mean of three estima-

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tions of serum parathyroid hormone was taken as the pretreatment control value. Further estimations of parathyroid hormone were made on at least two occasions in each patient, at eight and 12 months after the start of treatment.

All patients started treatment with $1-\alpha\text{-OHD}_3$ in a dose of $1\text{ }\mu\text{g/day}$, and the dose was adjusted in each patient according to the plasma calcium response. During the study the dose of $1-\alpha\text{-OHD}_3$ varied from $1.0\text{ }\mu\text{g/week}$ to $3.0\text{ }\mu\text{g/day}$. All the patients were treated for one year and in some treatment was continued for 18 months.

Results

Clinically, none of the patients had severe bone disease, but symptomatic improvement was noted in those with minor pains.

An example of the effect of treatment with $1-\alpha\text{-OHD}_3$ is shown in fig 1. Initially the patient received $1\text{ }\mu\text{g}$ of $1-\alpha\text{-OHD}_3$ daily and the dose was increased to $2\text{ }\mu\text{g}$ after five months. During the first eight months there was little biochemical response, but subsequently the plasma calcium concentration gradually rose until, at 16 months, he was hypercalcaemic. Plasma alkaline phosphatase fell and was normal at 16 months. Similarly, the concentration of parathyroid hormone fell progressively; at 12 months it was $1.05\text{ }\mu\text{g/l}$ and at sixteen months it was $0.84\text{ }\mu\text{g/l}$. Radiological improvement, though not complete healing, occurred during this time.

Since all the patients had been treated for at least one year, it is convenient to consider the results after one year's treatment (fig 2).

Plasma calcium—This increased significantly from $2.35 \pm (\text{SE of mean}) 0.05\text{ mmol/l}$ ($9.4 \pm 0.2\text{ mg/100 ml}$) before treatment to $2.67 \pm 0.04\text{ mmol/l}$ ($10.7 \pm 0.16\text{ mg/100 ml}$) at one year ($P < 0.001$). During the 12-month study plasma calcium concentrations rose in 13 of the patients; but because of changes in the dose of $1-\alpha\text{-OHD}_3$, only 10 of the patients were hypercalcaemic one year after starting treatment. In only two patients was there no significant change in the plasma calcium concentration throughout the study, and in two patients the plasma calcium concentration rose but remained within the normal range.

Plasma inorganic phosphorus concentration increased significantly ($P < 0.02$) from $1.28 \pm 0.10\text{ mmol/l}$ ($4.0 \pm 0.31\text{ mg/100 ml}$) to $1.72 \pm 0.14\text{ mmol/l}$ ($5.3 \pm 0.43\text{ mg/100 ml}$).

Plasma alkaline phosphatase was initially increased in 12 patients; it fell in 11 of these and became normal in 7 at one year. In nine patients a transient rise or "flare" of alkaline phosphatase occurred shortly after starting treatment with $1-\alpha\text{-OHD}_3$ or increasing the dose.

Serum parathyroid hormone—Before treatment the concentration

FIG 1—Example of the response in a patient treated with $1-\alpha\text{-OHD}_3$. Shaded areas represent normal ranges.
Conversion: SI to traditional units—Phosphorus: $1\text{ mmol/l} \approx 3.1\text{ mg/100 ml}$. Calcium: $1\text{ mmol/l} \approx 4\text{ mg/100 ml}$.

FIG 2—Effect of $1-\alpha\text{-OHD}_3$ on plasma calcium, plasma inorganic phosphorus, plasma alkaline phosphatase, and serum parathyroid hormone in 14 patients treated for one year. Dotted lines indicate normal ranges.

was raised in all patients (mean $4.74 \pm 0.58\text{ }\mu\text{g/l}$). At eight months this had fallen to $3.02 \pm 0.58\text{ }\mu\text{g/l}$ and at 12 months to $1.74 \pm 0.40\text{ }\mu\text{g/l}$ ($P < 0.001$). In eight patients serum parathyroid hormone concentrations became normal. In the one patient in whom alkaline phosphatase rose progressively the serum parathyroid hormone concentration did not change.

Improvement occurred in each of the 10 patients with radiological evidence of phalangeal erosions, and the lesions completely resolved in six. In one of these patients lesions of severe rickets also healed. Metastatic calcification was unaffected by treatment.

Discussion

Treatment of renal osteodystrophy with standard forms of vitamin D such as calciferol (vitamin D_2) has not proved entirely satisfactory, possibly because of impaired $1-\alpha$ -hydroxylation in the kidney of the 25-hydroxylated derivative formed in the liver. In support of this suggestion is the fact that the formation of $1,25\text{-(OH)}_2\text{D}_3$ appears to be impaired in chronic renal failure,⁷ and plasma $1,25\text{-(OH)}_2\text{D}_3$ concentrations are reduced in uraemic subjects.⁸ This hypothesis must, however, be accepted with caution since some anephric patients undergoing regular haemodialysis seem not to get osteomalacia.⁹ Theoretically such a metabolic block could be bypassed by giving $1-\alpha\text{-OHD}_3$, which is converted to $1,25\text{-(OH)}_2\text{D}_3$ in the liver, or by giving $1,25\text{-(OH)}_2\text{D}_3$ itself. Only recently have these compounds been synthesised in large enough quantities to enable their long-term use.

All our patients had secondary hyperparathyroidism. Some may also have had osteomalacia, but bone biopsies were not performed to establish this. In microgram doses 1- α -OHD₃ proved very effective and was capable of increasing plasma calcium and phosphorus concentrations and decreasing plasma alkaline phosphatase and serum parathyroid hormone concentrations. An increase in plasma calcium was expected but some of the other changes merit further consideration.

The increase in the plasma phosphorus concentration was not due to any reduction in the intake of aluminium hydroxide. Neither was it likely to have been due to the renal consequences of parathyroid hormone suppression, for our patients were effectively anuric. It probably resulted from increased intestinal phosphorus absorption caused by 1- α -OHD₃. Starting treatment or increasing the dose of 1- α -OHD₃ often increased the plasma alkaline phosphatase concentration, which subsided within a month. A similar "flare" is common in other forms of osteomalacia or rickets treated with vitamin D and does not indicate treatment failure.

The reduction in serum parathyroid hormone concentration, which fell to normal in over half the patients, was striking. It was accompanied by improvement and often disappearance of radiological phalangeal erosive changes attributable to hyperparathyroidism. We cannot be certain that the osteomalacic component of our patients' osteodystrophy responded so well. It has been suggested that the osteomalacic component is more resistant to treatment with 1- α -OHD₃.¹⁰ The mechanism whereby circulating parathyroid hormone was reduced is unknown. In general there was a rise in plasma calcium, which may have inhibited secretion of parathyroid hormone. Hypercalcaemia itself, however, was not essential for the fall of parathyroid hormone concentration. In one patient the serum parathyroid hormone concentration fell, even though the plasma calcium concentration rose only slightly and remained within the normal range. In another patient serum parathyroid hormone and plasma alkaline phosphatase concentrations fell progressively without any detectable change in the plasma calcium concentration, which remained normal during the study. Therefore a derivative of vitamin D may directly suppress secretion of parathyroid hormone by the parathyroid glands.

The effect of 1- α -OHD₃ on parathyroid activity and bone

appears to be slow and the response to treatment must be assessed over at least several months. It has been suggested that 1- α -OHD₃ is safer to use than the natural compound 1,25-(OH)₂D₃ since it is hydroxylated in the liver. In animals this step appears to be inhibited by the product of hydroxylation itself and may act as a potential safety factor.

Episodes of severe hypercalcaemia requiring a reduction of dose or temporary cessation of treatment occurred in six patients. In three the hypercalcaemia was associated with pruritus but with no other serious effects, and, in particular, radiologically detectable ectopic calcification was not produced. Hypercalcaemia was most likely to occur when renal osteodystrophy had improved, as shown by a fall in plasma alkaline phosphatase, radiological improvement, and a return of parathyroid hormone concentrations to near normal. It might, however, develop at any time during treatment with 1- α -OHD₃, irrespective of the dose given, and careful monitoring of plasma calcium is therefore essential.

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Enhanced allergic tissue injury in Goodpasture's syndrome by intercurrent bacterial infection

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Summary

Studies of 16 relapses in seven patients receiving treatment for Goodpasture's syndrome showed that intercurrent bacterial infection seemed to be the precipitating event in 13 cases, whereas a rising antibody titre to glomerular basement membrane was responsible in only one.

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This association between infection and relapse in Goodpasture's syndrome has several implications for the pathogenesis of antibody-mediated tissue damage, and, clearly, more experiments are needed. Whatever the explanation, however, prevention and early diagnosis and treatment of infection in anti-GBM disease are important.

Introduction

We have recently developed a regimen of intensive plasma exchange and cytotoxic drugs for treating Goodpasture's syndrome associated with antibody to glomerular basement membrane (GBM),¹ and this has provided an opportunity to study an unusually large number of patients. An important feature of this project has been monitoring disease by serial