COMPARISON OF 1,25(OH)$_2$D$_3$ AND 24,25(OH)$_2$D$_3$ IN THE LONG-TERM TREATMENT OF RENAL OSTEODYSTROPHY

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Summary

24,25(OH)$_2$D$_3$ has been compared with 1,25(OH)$_2$D$_3$ in the treatment of renal osteodystrophy. Treatment with 24, 25(OH)$_2$D$_3$ 2µg/day for 5–7 months was accompanied by deterioration in clinical, biochemical, radiological and histological features of osteodystrophy with no increase in Ca absorption. In contrast, treatment with 1,25(OH)$_2$D$_3$ 0.25–1µg/day for 6–15 months resulted in rapid improvement in clinical, biochemical, radiological and histological features and a return of Ca absorption to normal. It is concluded that in the dose used 24,25 (OH)$_2$D$_3$ alone is not an effective treatment for renal osteodystrophy.

Introduction

Renal osteodystrophy remains a cause of considerable morbidity amongst patients undergoing long-term haemodialysis [1]. The aetiology [2] of the condition is complex but it is now generally acknowledged that there are three main interrelated pathogenetic mechanisms i) Secondary hyperparathyroidism due to skeletal resistance to PTH [3] and possibly PO$_4$ retention, ii) Relative or absolute lack of vitamin D due to impaired production of active renal metabolites of vitamin D$_3$ [4] and resistance to vitamin D action secondary to uraemia, and iii) Progressive skeletal demineralisation due largely to hyperparathyroidism and possibly other factors such as acidosis and heparin [1].

A number of metabolites of vitamin D$_3$ have now been identified which have known or putative effects on Ca metabolism. 1,25(OH)$_2$D$_3$ has been extensively studied in both animals and man and possesses all of the bidental activities associated with vitamin D i.e. it stimulates Ca absorption, raises serum Ca, suppresses PTH production and promotes mineralisation of osteoid [5,6].

The actions of 24,25(OH)$_2$D$_3$ are more controversial. It is present in serum in concentrations up to 100 times those of 1,25(OH)$_2$D$_3$ so that a biological role is possible. The exact nature of this is not clear but studies in animals and man have suggested that 24,25(OH)$_2$D$_3$ promotes Ca absorption and skeletal mineral-
isation [7–11].

It seemed appropriate to explore the possibility that 24,25(OH)\(_2\)D\(_3\) might be of therapeutic value in the treatment of renal osteodystrophy. We have therefore compared 1,25(OH)\(_2\)D\(_3\) and 24,25(OH)\(_2\)D\(_3\) in a group of maintenance haemodialysis patients.

Methods

A total of 18 patients aged 22–57 (mean 41.8 ± 12.2 years) maintained on haemodialysis for 8–125 months (mean 45 ± 34.2) were studied. Patients were dialysed for 12–18 hours/week in 2 or 3 sessions against an acetate buffered dialysate with Ca concentration of 1.5mmol/L. All patients received sufficient aluminium hydroxide (Aludrox, Wyeth) to maintain predialysis serum PO\(_4\) below 2mmol/L and calcium supplements as calcium carbonate B.P. 2g/day if not hypercalcaemic.

Patients were randomly assigned to one of two treatment groups. Group I, comprising 11 patients, received 24,25(OH)\(_2\)D\(_3\) 2\(\mu\)g/day in 2ml 50:50 ethanol:propanediol for 5–7 months. Group 2, comprising 7 patients, received 1,25(OH)\(_2\)D\(_3\) 0.25–1\(\mu\)g/day in capsule form for 6–15 months. The starting dose was 1\(\mu\)g/day and the maintenance dose was the minimum compatible with normocalcaemia.

Investigations included estimation of serum Ca, PO\(_4\), alkaline phosphatase (alk. phos.), PTH, 25(OH)D\(_3\) and 1,25(OH)\(_2\)D\(_3\) at six weekly intervals throughout a run-in period of 3–6 months, and during treatment. Ca,PO\(_4\) and alk. phos. were measured in the Department of Chemical Pathology, University of Aberdeen using a SMAC autoanlyser (Technicon U.K. Ltd). 25(OH)D\(_3\) was assayed by Dr BF Allam, Department of Biochemistry, Stobhill General Hospital, Glasgow by a competitive protein binding method [12]. Serum PTH was measured by Dr JLH O’Riordan, Middlesex Hospital, London using a recently described human specific amino-terminal radioimmunoassay [13]. The upper limit of normal for this assay is 120pg/ml.

Calcium absorption studies were performed on 10 patients before and during treatment with 1,25(OH)\(_2\)D\(_3\) (4 patients) or 24,25(OH)\(_2\)D\(_3\) (6 patients). Patients received an oral dose of 10\(\mu\)Ci 47Ca with 72mg Ca gluconate carrier. Peak Ca absorption was measured on blood samples taken at 1 and 2 hours after ingestion of the isotope and whole body retention was followed over the next 7 days by total body counting, taking the retention figure obtained by counting at 1½ hours as 100%.

Qualitative bone histology was assessed on full thickness iliac crest bone biopsies obtained before and after treatment. Radiological skeletal surveys were also obtained before and after treatment.

Bone mass was assessed by serial partial neutron activation analysis (NAA) of a hand and estimates of bone mineral content (BMC) of the distal third of the radius using a Norland-Cameron 178 bone mineral analyser. These methods have been in use in our laboratory for a number of years and are known to give complementary results [1,14].

Statistical analysis of biochemical data was by paired t-test and of NAA and BMC by regression analysis.
Results

In the 1,25(OH)₂D₃ treated group all 4 patients with clinical bone disease improved symptomatically during treatment (Table I). Mean serum Ca rose significantly and serum AP and PO₄ fell, though not significantly (Table II). PTH levels

<table>
<thead>
<tr>
<th>Histology</th>
<th>Symptoms</th>
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<tr>
<td>Improved</td>
<td>Unchanged</td>
</tr>
<tr>
<td>1,25(OH)₂D₃</td>
<td>5/7</td>
</tr>
<tr>
<td>treated</td>
<td></td>
</tr>
<tr>
<td>24,25(OH)₂D₃</td>
<td>0/11</td>
</tr>
<tr>
<td>treated</td>
<td></td>
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</tbody>
</table>

* Normal throughout  
† Asymptomatic throughout  
‡ 5/11 developed symptoms for first time during treatment

1,25(OH)₂D₃ and 24,25(OH)₂D₃ in renal osteodystrophy = effects on symptoms and bone histology

<table>
<thead>
<tr>
<th>TABLE II</th>
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<tr>
<td>1,25(OH)₂D₃</td>
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<td>treated</td>
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<td>24,25(OH)₂D₃</td>
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1,25(OH)₂D₃ and 24,25(OH)₂D₃ in renal osteodystrophy: Biochemistry-statistical analysis by Student’s t-test

fell in 5/7 and were unchanged in the remaining two. Five/seven showed histological improvement and the remaining two patients had normal bone histology throughout the study (Table I). Radiological features of bone disease improved in 5/7, and were normal throughout in 2/7.

In the 24,25(OH)₂D₃ treated group 10/11 patients either became symptomatic for the first time or became symptomatically worse during treatment (Table I). Mean serum Ca, PO₄ and alk. phos. were unchanged though alk. phos. did tend to rise in some patients (Table II). PTH was unchanged in 3/11 and rose in the remaining 8/11. In 6/11 patients histological progression of bone disease was apparent whilst in 4/11 histology was unchanged (Table I). One patient refused a second bone biopsy but was clinically and biochemically worse. Radiological improvement was not seen in any patients in this group, whilst X-ray features were worse in 3/11 and unchanged in 8/11, being normal throughout in 2/11.

All 10 patients who underwent Ca absorption studies had low peak Ca absorp-
tion and 7 day Ca retention before treatment. Following $1,25(\text{OH})_2\text{D}_3$ 0.25–1µg/day for 6–15 months peak Ca absorption and 7 day Ca retention returned to normal in all 4 patients. All 6 patients treated with $24,25(\text{OH})_2\text{D}_3$ µg/day for 4–6 months showed no improvement in peak Ca absorption or 7 day Ca retention.

Serial NAA and BMC revealed a tendency towards demineralisation that was unaffected by $24,25(\text{OH})_2\text{D}_3$. Although the rate of bone loss was diminished by $1,25(\text{OH})_2\text{D}_3$ therapy the demineralisation trend was not reversed.

**Discussion**

Our results demonstrate that, in the dose used, $24,25(\text{OH})_2\text{D}_3$ alone is ineffective in reversing the clinical, biochemical, radiological and histological features of renal osteodystrophy or in preventing progressive skeletal demineralisation. We have failed to show any effect of $24,25(\text{OH})_2\text{D}_3$ on promoting Ca absorption in end-stage renal failure.

Most of the evidence that $24,25(\text{OH})_2\text{D}_3$ does have an important physiological role is, at present, indirect. Bordier [15] showed that in vitamin D deficient man, normal mineralisation was produced by $25(\text{OH})\text{D}_3$ but not $1,25(\text{OH})_2\text{D}_3$ suggesting that a metabolite other than $1,25(\text{OH})_2\text{D}_3$, was active in this respect. The work of Miravet [10], Corvol [8] and Ornoy [9] in various animal species lends valuable direct and indirect support to this concept while Kanis has reported [11] that $24,25(\text{OH})_2\text{D}_3$ produces a fall in serum Ca in normal man without any increase in urinary Ca, suggesting a positive effect on skeletal Ca accretion.

The effects of $1,25(\text{OH})_2\text{D}_3$ were rather more predictable. Clinical, biochemical, radiological and histological improvement was noted in most, but not all, patients. Hypercalcaemia was a problem in this group and the very low maintenance doses of $1,25(\text{OH})_2\text{D}_3$ needed to keep serum Ca within acceptable limits may have been insufficient to produce maximal PTH suppression in all patients. It is of interest that while the rate of bone loss measured by NAA and BMC slowed during $1,25(\text{OH})_2\text{D}_3$ therapy the trend was not reversed i.e. the patients did not remineralise.

It is apparent that $1,25(\text{OH})_2\text{D}_3$ alone is not effective in reversing all of the features of renal osteodystrophy in all patients. The development of hypercalcaemia and sub-maximal PTH suppression may be the main limiting factors but the lack of a normal mineralising effect is also likely to be important.

A future approach might be to combine therapy with $1,25(\text{OH})_2\text{D}_3$ and $24,25(\text{OH})_2\text{D}_3$ to promote effective Ca absorption and suppression of PTH and effective skeletal mineralisation. Such studies are currently in progress in our laboratory.

**Acknowledgments**

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We are also grateful to Roche Products for providing the $1,25(\text{OH})_2\text{D}_3$ and $24,25(\text{OH})_2\text{D}_3$, and for their support.
References

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Open Discussion

PARSONS (London) Why have you presented results with no dose response curve at all? Why did you choose 2μg as the optimum dose of 24,25? You had already stated that the concentration in the plasma was 100 times that of 1,25 and why did you not choose 20μg?

MUIRHEAD We are looking for a physiological response and the 2μg dose of 24,25 that we chose has been suggested as being comparable to the physiological output of 24,25. In addition the clearance of 24,25 from blood is very much slower than that of 1,25. We are in fact awaiting 24,25 levels on our patients which would have assisted clarification of this point, but we would anticipate that they would not fall too far short of normal levels. However I agree that it might have been more useful to try other doses.

ULMANN (Paris) What were the values of plasma 1,25 and 24,25 during your study? Did you measure 24,25 during treatment with 1,25 and vice versa?

MUIRHEAD As I just indicated, we are awaiting the results of these studies. In answer to your question — yes, we did do 24,25 during 1,25 administration and vice versa. There are some preliminary 1,25 results available. In the patients so far studied all have had undetectable 1,25 levels in the untreated state which have not surprisingly risen following 1,25 therapy.