USE OF 1,25(OH)$_2$-VITAMIN D$_3$ TO SEPARATE ‘TYPES’ OF RENAL OSTEODYSTROPHY


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Summary

Patients with severe symptomatic renal osteodystrophy were treated with either 1,25(OH)$_2$D$_3$ or 1α(OH)D$_3$. In 39 instances, there was either reversal of symptoms and/or a marked fall in plasma alkaline phosphatase. Bone biopsies showed improvement of either osteomalacia or osteitis fibrosa, and serum iPTH often fell. In thirteen patients, no improvement occurred. In seven patients, bone biopsy disclosed osteomalacia, and serum iPTH was normal or only slightly elevated. Thus, there was a defect in mineralisation, apparently unrelated to the lack of 1,25(OH)$_2$D$_3$ and in the absence of evidence of phosphate depletion. The other ‘treatment failure’ group showed osteitis fibrosa on biopsy and iPTH levels were markedly elevated. They are presumed to have marked secondary hyperparathyroidism. These ‘treatment failure’ groups had higher pre-treatment levels of serum Ca and Mg than in those showing a favourable response; also, hypercalcaemia developed rapidly during 1,25(OH)$_2$D$_3$ treatment. Thus, 1,25(OH)$_2$D$_3$ is efficacious in treating symptomatic osteodystrophy in many uraemic patients, and in other patients, it may help identify bone disease of other, as yet unknown, pathogenesis.

Introduction

Treatment with the active vitamin D compound, 1,25-dihydroxy-vitamin D$_3$ (1,25(OH)$_2$D$_3$), or its synthetic analogue, 1α-hydroxy-vitamin D$_3$ (1α(OH) D$_3$), can reverse many of the abnormalities of divalent ion metabolism observed in uraemia1,2,3. Thus, the balance for calcium and phosphorus improve, intestinal Ca absorption is enhanced, and hypocalcaemia is corrected. Moreover, reports suggest that these sterols can reverse the skeletal manifestations
of secondary hyperparathyroidism and improve the osteomalacia in many uraemic patients. The present report describes our experience with managing overt renal osteodystrophy in uraemic patients using 1,25(OH)₂D₃.

Materials and Methods

Forty-seven patients, 38 men and 9 women, aged 15 to 76 years, received treatment with 1,25(OH)₂D₃ (44 studies) or 1α(OH)D₃ (7 studies). Since the results with 1α(OH)D₃ and 1,25(OH)₂D₃ were similar, all data have been pooled. Thirty-eight patients were under treatment with maintenance haemodialysis: mean duration, 4.0 years. Ten patients had advanced stable chronic renal failure, but creatinine clearances were below 15 ml/min. Eight patients had received a renal transplant that had functioned for 2–4 years but then undergone rejection. Twenty-two patients, representing 7% of the dialysis patients under treatment, were from the dialysis units in our hospitals (VA Wadsworth Hospital, Center, Seattle VA Hospital, and St Francis Hospital). Twenty-five patients were referred to us from elsewhere because of symptomatic skeletal disease.

Treatment was initiated because of severe symptoms, including skeletal pain, fractures, muscular weakness, and symptomatic hypocalcaemia, in 35 patients. Elevated alkaline phosphatase levels, abnormal bone biopsies, and/or marked hypocalcaemia were present in twelve patients who lacked serious symptoms. Previous management of altered divalent ion metabolism included aluminium hydroxide or carbonate (95–100%), oral supplements of Ca (57%), treatment with pharmacological quantities of a vitamin D preparation (ie, vitamin D₂, 1.25 mg/day, or dihydrotachysterol, 0.125–0.6 mg/day) in 41%, or parathyroid surgery in 16%.

The 1,25(OH)₂D₃ was prepared biosynthetically or chemically by Hoffmann-La Roche (Nutley, NJ) and was given as a single oral daily dose. Because of limited availability of the sterol, doses were 0.14 to 0.28 µg/day at the outset of the study. More recently, the initial therapy has been 0.25 µg/day for 1–2 weeks, and then 0.5 to 1.0 µg/day. For the entire group of patients, the dose of 1,25(OH)₂D₃ averaged 0.62 µg/day, while that of 1α(OH)D₃ was 1.60 µg/day. The duration of treatment averaged 22 weeks (range 2–90 weeks). Dialysis was carried out thrice weekly with dialysate containing 6.0–7.0 mg/dl of Ca.

At intervals of 1–4 weeks, clinical evaluation and measurements of serum Ca, P, magnesium, and alkaline phosphatase were made. Immunoreactive parathyroid hormone (iPTH) was measured in most patients at monthly intervals using methods and antisera described elsewhere. An iliac crest bone biopsy was obtained before treatment in 45 patients. Skeletal X-rays were obtained before and at 6 monthly intervals during treatment. Symptoms and signs of skeletal pain and muscular weakness were graded on a 'global disability score', derived from the activities of the patients; this was evaluated before and during treatment in all patients and 2–5 months after withdrawal of treatment in sixteen patients.
Results

Skeletal pain was present in 38 patients; such pain often began subsiding by 1–3 weeks after initiation of treatment, and it totally disappeared in 55% of afflicted patients. However, there was no change in twelve patients. Muscular weakness, typical of that reported in osteomalacia, was present in 26 patients. Muscle strength improved in 19 patients and was unchanged in seven. Among the 38 patients with significant symptoms, 23 noted improvement, while thirteen failed to improve. In several of the latter, treatment was discontinued because of hypercalcaemia. These patients are considered as ‘treatment failures’. Thirteen patients lacked serious symptoms. The ‘global disability scores’, before treatment, upon completion of a treatment course, and 2–4 months after withdrawal of treatment, are shown in Figure 1.

Figure 1. Global disability score in symptomatic patients responding to 1,25(OH)\(_2\)D\(_3\) and followed for 2–5 months after withdrawal of treatment. The scores for disability vary from 1, symptoms only with strenuous activity, to 5, totally disabled, restricted to bed or wheelchair.

Despite the arbitrary division of the patients on the basis of their clinical response, there were distinct biochemical differences between those who responded and the ‘treatment failure’ group. These data are shown in Table I. In this table, the ‘treatment failure’ patients have been grouped according to the predominant skeletal pathology seen on a bone biopsy. Serum Ca increased in all groups, but the pre-treatment levels were higher in the ‘treatment failure’ group. Alkaline phosphatase decreased only in the responders and remained
### TABLE 1. Serum Biochemical Data in Patients with Symptomatic Osteodystrophy Treated with 1,25(OH)₂D₃ or Levo(OH)₂D₃

<table>
<thead>
<tr>
<th>TREATMENT FAILURES</th>
<th>C</th>
<th>T</th>
<th>OF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n = 12</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>n = 7</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>n = 5</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>RESPONDERS</strong></td>
<td><strong>n = 24</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>C</th>
<th>C</th>
<th>T</th>
<th>T</th>
<th>OF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sc₃ (mg/dl)</td>
<td>9.00 ± 0.26</td>
<td>10.40 ± 0.19</td>
<td>9.90 ± 0.19</td>
<td>11.63 ± 0.33</td>
<td>12.36 ± 0.55</td>
</tr>
<tr>
<td>Sc₅ (mg/dl)</td>
<td>4.39 ± 0.28</td>
<td>4.75 ± 0.32</td>
<td>4.75 ± 0.32</td>
<td>5.48 ± 0.39</td>
<td>5.36 ± 0.36</td>
</tr>
<tr>
<td>Alk phos (IU)</td>
<td>240 ± 75</td>
<td>139 ± 32</td>
<td>139 ± 32</td>
<td>160 ± 22</td>
<td>186 ± 12</td>
</tr>
<tr>
<td>Smg (mg/dl)</td>
<td>2.79 ± 0.15</td>
<td>3.28 ± 0.22</td>
<td>2.81 ± 0.09</td>
<td>3.17 ± 0.38</td>
<td>3.81 ± 0.44</td>
</tr>
</tbody>
</table>

* Bone biopsy not available in two cases
OM = serum Ca
C = pre-treatment; T = treatment
OF = skeletal lesion predominantly ostemala
Skeletal lesion predominantly osteitis fibrosa

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elevated in the other groups. For all patients, the mean serum P was $4.59 \pm 0.18$ before and $4.79 \pm 0.21$ mg/dl after treatment. There were no significant differences between the mean pre-treatment serum P levels of the three groups. There was a decrease in serum P during treatment in 23 instances, generally in those with a favourable response; this usually occurred within the 1–3 months of starting treatment, which probably reflects changes during a phase of rapid skeletal remineralisation. In 22 patients, serum P rose by 1.0 mg/dl or more; this usually occurred after 4–10 months of treatment and was sometimes coincident with a hypercalcaemic episode. This may be attributed, in part, to a prominent effect of $1,25(OH)_2D_3$ in stimulating intestinal absorption of P in uraemic patients$^{13}$.

The mean pre-treatment serum Mg was $2.97 \pm 0.11$ mg/dl for all patients, and there was no change with treatment. The mean serum Mg levels were significantly higher in the two 'treatment failure' groups than in the patients who showed a favourable response.

The pre- and post-treatment levels of alkaline phosphatase for the three groups are shown in Figure 2. There was a significant fall in the values in the

![Figure 2. Serum alkaline phosphatase levels in treatment groups categorised according to clinical response. C = control; T = treatment. Duration of treatment in weeks; geometric means are indicated by horizontal lines. The failure groups are indicated as 'no change' patients who improved with treatment and also in the asymptomatic patients. The levels did not change in the 'treatment failure' groups. Thus, a decrease in elevated alkaline phosphatase correlated with clinical improvement.

Serum iPTH levels, obtained before treatment, showed a rough correlation
with the type of bone histology found (Figure 3). In the symptomatic patients who responded to treatment, iPTH was 2 to 24-fold the upper normal limit before treatment. In half of these, iPTH decreased by 25% or more, and values returned to normal in 20%. The plasma iPTH levels were elevated in 11 of 13 asymptomatic patients; these fell to within the normal range during treatment in 40%.

![Figure 3. Serum iPTH levels indicated in multiples of the upper range of normal in relation to the major histologic feature seen in bone biopsy. OM = osteomalacia; OF = osteitis fibrosa](image)

The patients classified as 'treatment failures' seem to be of special interest. In seven, bone biopsies showed either 'pure' osteomalacia, with little or no increase in resorption or osteitis fibrosa, or osteomalacia predominated. Serum iPTH was normal in four and 2–6 times normal in the other patients. Three of these patients had undergone prior parathyroidectomy. The mean serum P was 4.7 mg/dl and provided little evidence for phosphate depletion. Also, three of these patients showed no improvement when therapy with Al(OH)₃ was reduced and serum P rose to 5–6 mg/dl. In five patients, the bone biopsy showed an increase in resorption surface and marrow fibrosis, with varying increases in the forming surfaces. Serum iPTH was generally higher in this group.

In all, 33 episodes of hypercalcaemia occurred during treatment of 20 patients. Within 1–3 days after withdrawal of treatment, serum Ca generally fell. Two patterns of hypercalcaemia were seen: in eleven patients, 23 episodes of hypercalcaemia occurred within the first eight weeks of treatment. Nine of
these patients are in the 'treatment failure' group, and hypercalcaemia developed with a daily dose below 0.5 μg/day in 17 instances. In eight other patients, 10 hypercalcaemia episodes developed after 4–15 months of treatment. In this group, pre-treatment serum Ca levels were lower and they had generally received higher daily doses of 1,25(OH)₂D₃. Under these circumstances, the hypercalcaemia occurred coincidentally with a fall of plasma alkaline phosphatase from 220 ± 51 IU to 87 ± 13 IU. It is believed that such hypercalcaemia occurred as remineralisation of the abnormal skeleton was complete or greatly slowed. In several patients from this group, treatment was resumed using a lower daily dose without subsequent difficulty.

Discussion

The present data point to the efficacy of 1,25(OH)₂D₃ in improving symptoms and reversing many of the biochemical features that exist in patients with symptomatic renal osteodystrophy. In some instances, the patients were able to walk after being totally bedridden. Improvement of myopathy, which resembles that described in vitamin D-deficiency, was prominent and gratifying. Improvement in symptoms correlated with a fall in serum alkaline phosphatase.

The present study also identifies two groups who failed to respond to 1,25(OH)₂D₃. In one group, very marked secondary hyperparathyroidism probably exists, and the administration of small amounts of 1,25(OH)₂D₃ caused hypercalcaemia. These patients may have marked parathyroid hyperplasia with relative non-suppressibility of the gland. In a second group, the skeletal biopsy revealed abundant unmineralised osteoid, little or no evidence of excess PTH action, and the appearance of an inactive skeleton. Serum iPTH levels were often low. Low levels of serum P were not seen in this group, unlike the observations of Pierides et al. The mechanism whereby serum Ca can be maintained in the high normal range despite low levels of iPTH is unknown. The administration of small doses of 1,25(OH)₂D₃ raised serum Ca levels, probably via increased intestinal Ca absorption, but led to no improvement of the skeleton. Also, we observed little or no evidence of improvement after dietary P intake was increased so that predialysis serum P levels were 5–7 mg/dl.

Serum Mg levels were slightly higher in the 'treatment failure' groups; serum Mg is known to correlate with skeletal Mg and our observations provide support for the theory that increased skeletal Mg may be detrimental to the skeleton in patients with uraemia.

Thus, the present data provide evidence for the clinical usefulness of 1,25(OH)₂D₃ as an effective agent capable of reversing severe manifestations of skeletal disease in uraemia. In addition, evaluation of the therapeutic response to 1,25(OH)₂D₃ may separate and identify patients with 'types' of renal osteodystrophy which arise due to pathogenic processes different from those believed to be predominant. Further studies will be necessary to identify the causes of bone disease in these patients.
Acknowledgments

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Open Discussion

DRUEKE (Paris) Would you think that different thyrocalcitonin levels could play a role in the different responses to 1,25 treatment in your patients? Have you had occasion to transplant some of the patients with severe bone pain, and did you see any improvement in these patients?

COBURN We do not have data on calcitonin in these patients. One of the patients with severe bone disease did have a kidney transplant one month ago
so we may have some experience with this soon. From the data Dr Madsen has presented, one might not achieve total recovery of bone disease; however, if there was partial improvement that would suggest that some factor, related to the presence of normal kidney tissue or kidney function, was responsible.

NAIK (Birmingham) I know that you have had recurrence of hyperparathyroidism in some patients who presumably had subtotal parathyroidectomy. Do you recommend total parathyroidectomy for these patients who have secondary hyperparathyroidism?

COBURN No, because I think the problems associated with total parathyroidectomy are greater than the risk of recurrence of secondary hyperparathyroidism. In one or two of the patients who did show recurrence, we were unable to demonstrate marked hyperphosphataemia or hypercalcaemia as the recurrence developed. Some groups in the USA are doing a total parathyroidectomy and transplant part of the tissue into the forearm, so that it is more accessible to subsequent surgery.

WINNEY (Edinburgh) With regard to the patients with predominantly secondary hyperparathyroidism who did not respond to the treatment, was the severity of the hyperparathyroidism greater than in the group who did respond? Could either the dialysate calcium or dietary calcium intake have been a factor influencing the dosage tolerance in the patient?

COBURN There was some variation in both of the groups. The dialysate calcium was between 1.5 and 1.75 mmol/L, but many of the patients have been dialysed for a number of years, and they may have undergone dialysis for a period with a bath of 1.25 mmol/L but were using a higher level for several years before the bone disease developed. The dietary calcium intake varied, but we were not able to detect any difference between those who responded, and those who did not.