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OSTEOPENIA – AN ASSESSMENT OF LONG-TERM THERAPY WITH VITAMIN D ANALOGUES

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Summary

Renal bone disease was assessed for an average of 5.5 years in 9 patients on maintenance haemodialysis. The investigative methods included serial biochemical estimations, radiographic skeletal surveys and quantitative bone histology. Repeated bone mineral analyses and neutron activation analyses of a hand were also performed in order to monitor changes in skeletal calcium content.

Before treatment, progressive osteodystrophy was demonstrated by all techniques. Following therapy with the vitamin D analogues, all patients noted symptomatic improvement; serum alkaline phosphatase reverted to normal and serum parathyroid hormone concentrations decreased. Radiographically, subperiosteal erosions healed while the histological features of osteomalacia and osteitis fibrosa were abolished. Both bone mineral and neutron activation analyses indicated that progressive skeletal demineralisation had been halted. However, a sustained increase in the overall mineral content of bone was not demonstrated. Thus, vitamin D therapy although improving the biochemical, radiological, and histological features of renal osteodystrophy may not restore bone mass to osteopenic bone.

Introduction

The metabolic bone diseases associated with chronic renal failure remain an important cause of patient morbidity. Many patients on maintenance haemodialysis eventually develop signs, or less commonly, symptoms of renal osteodystrophy [1]. Histologically, the features of osteitis fibrosa, osteomalacia and osteosclerosis may be noted individually or in any combination [2].

During the last ten years the metabolic pathway of vitamin D has been traced. It is now appreciated that cholecalciferol undergoes hydroxylation in the liver to produce 25(OH) vitamin D₃ and a second hydroxylation in the kidney to form the active end-hormone 1,25(OH)₂ vitamin D₃ [3]. Lack of this substance in the
plasma of patients with renal insufficiency thus provides a rational explanation for many of the features of renal bone disease [4]. However, the extent to which therapy with 1,25(OH)₂ vitamin D₃ or its analogue 1α(OH) vitamin D₃ can reverse progressive osteodystrophy is not yet established. The aim of the present investigation was to assess the effect of long-term therapy with vitamin D analogues on the progressive renal bone disease of patients with chronic renal failure on maintenance haemodialysis.

Patients and Methods

The four men and five women in this study had a mean age of 33 years and, at the end of the trial, had been established on maintenance haemodialysis for an average of 7.3 years. They were studied for a mean time of 2.6 years before and 2.2 years during treatment with one of the vitamin D analogues. Eight patients were treated with 1α(OH) vitamin D₃ and one with 1α(OH)₂ vitamin D₃. The dosages of the vitamin D derivatives were adjusted as required to maintain the serum calcium concentrations within normal limits; aluminium hydroxide was prescribed as necessary to control hyperphosphataemia. Despite these measures, however, three patients required parathyroidectomy for sustained hypercalcaemia.

The investigative methods included serial biochemical estimations of serum calcium, phosphate, alkaline phosphatase and parathyroid hormone concentrations. Radiographic skeletal surveys and iliac crest bone biopsies were repeated at intervals of six months; quantitative bone histology was obtained on the biopsy samples. Six times per year each patient underwent both bone mineral analysis of the radius and neutron activation analysis of a hand. Bone mineral analysis is a densitometric technique in which the attenuation in the gamma radiation transmitted from a collimated ¹²⁵I source to the lower third of the radius is correlated with the overall mineral content of bone. Neutron activation analysis, however, measures specifically the calcium content of the tissues irradiated — in this case a hand. A small 25 Ci source of ²⁴¹Am and Be was used to provide the required neutron flux. The gamma radiation from ⁴⁹Ca, produced from stable ⁴⁸Ca by neutron capture, was detected and quantitated by two sodium iodide crystals linked to a multi-channel analyser. Changes in the calcium content of the hand were thus monitored by alterations in the amount of detected radiation.

Results

Before treatment began all patients noted muscle weakness and had (a) elevated serum concentrations of alkaline phosphatase and parathyroid hormone; (b) radiological subperiosteal erosions; (c) histological features of osteomalacia and osteitis fibrosa; (d) evidence of progressive skeletal demineralisation by both bone mineral analyses and neutron activation analyses.

After therapy with one of the vitamin D derivatives all patients claimed a symptomatic improvement in their muscle weakness. Serum alkaline phosphatase concentrations reverted to normal (Figure 1); serum parathyroid hormone con-
Figure 1. Serum concentration of alkaline phosphatase before and after treatment with one of the vitamin D derivatives. ⋄—⋄ indicates those patients treated with vitamin D; X—X indicates the 3 patients who in addition to vitamin D therapy underwent parathyroidectomy. The horizontal interrupted line indicates the upper limit of the normal range for serum alkaline phosphatase concentration.

Concentrations decreased considerably but remained consistently within normal limits in those patients subjected to parathyroidectomy (Figure 2). The radiographic subperiosteal erosions healed. Histological features of osteomalacia and osteitis fibrosa were abolished, osteoid volume decreased to within normal limits (Figure 3), and bone morphology returned to normal. The results from both bone
Figure 2. Serum concentrations of parathyroid hormone before and after treatment with one of the vitamin D derivatives. ●—● indicates those patients treated with vitamin D; X—X indicates the 3 patients who in addition to vitamin D therapy underwent parathyroidectomy. The horizontal interrupted line indicates the upper limit of the normal range for serum parathyroid hormone concentration.

Mineral and neutron activation analyses indicated that the process of progressive skeletal demineralisation had been halted. However, a sustained increase in the overall mineral content of bone was not demonstrated by either technique.
Figure 3. Assessment of osteoid volume before and after treatment with one of the vitamin D derivatives. ●—● indicates those patients treated with vitamin D; X—X indicates the 3 patients who in addition to vitamin D therapy underwent parathyroidectomy.

Discussion

The results presented in this paper confirm that therapy with either 1,25(OH)₂ vitamin D₃ or 1α(OH) vitamin D₃ produces a substantial improvement in the biochemical, radiological and histological features of renal osteodystrophy. In three patients, however, parathyroidectomy was required to control elevated plasma calcium concentrations before treatment with one of the vitamin D analogues could be safely administered. All nine patients noted a symptomatic improvement while on treatment with vitamin D.

The technique of partial body neutron activation analysis used in this investigation has been shown to be a more sensitive indicator of the rate of progression or healing in renal bone disease than either skeletal radiography or bone mineral
analysis. The coefficient of variation, assessed by repeated measurements of anatomical specimens, is between 4% and 5% for clinical studies. In three patients with particularly rapid skeletal demineralisation, a significant reduction in the rate of calcium loss was noted when vitamin D treatment began. Nevertheless a sustained increase in the overall mineral content of bone was not demonstrated in any of the patients by this technique nor by the method of bone mineral analysis. As two of the patients have experienced fractured bones following only minor trauma it is unlikely that bone mass has returned to normal in these patients. A degree of osteopenia may remain.

Although osteoporosis has been considered to be relatively uncommon in patients with chronic renal failure, it was observed in 11 out of 46 patients with chronic renal failure by Ingham et al [6] and was also monitored in patients on maintenance haemodialysis by Henderson et al [7]. The causes of osteoporosis in patients on maintenance haemodialysis are not fully established but it is likely that such factors as heparin, immobilisation, malabsorption of calcium from the gastrointestinal tract, and a slow loss of calcium from the patient into the dialysis fluid are important. From this study, however, it is concluded that vitamin D therapy, although improving the biochemical, radiological, and histological features of renal bone disease, may not restore bone mass to osteopenic bone.

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References

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Open Discussion

FOURNIER (Amiens) How can you be sure that measurement of the calcium content of the hand by neutron activation (NA) accurately reflects the calcium content of the bone? In our experience based on 18 patients treated for one year with 1,25(OH)₂D₃, we found that the calcium content of the hand measured by NA increased in most of the patients whereas their osteitis fibrosa assessed by histomorphometry did not improve. Furthermore soft tissue calcifications appeared on hand X-rays in one case. Therefore we are afraid that the increase in calcium content was mainly due to increased soft tissue calcification.

CATTO Could I take these points separately? First of all, our results seem to be the other way round; the opposite in fact. We seem to have improvement in many
of the factors that we have measured. However, two of the patients have had broken bones and we have been unable to show an increase in the overall mineral content of bone. Secondly the activation technique in the hand of course measures calcium gravities in both soft tissue and bone. We chose the hand because radiologically the features of bone disease are frequently seen there first. Moreover the ratio of soft tissue to bone is probably less in the hand than in any other suitable organ. So far, we have not had a great deal of difficulty with extraskeletal calcification and I don't think that factor by itself explains our results. The final point I want to make is that even if one ignores the results from neutron activation analysis, we still have people who seem to have bones that have improved by many of the standards that we are looking at and yet break. I think there probably is a genuine clinical problem present here.

WINNEY (Edinburgh) Your results appear to be contradictory. You demonstrate an increase of bone mineral as evidenced by healing of erosions and yet no increase in calcium content as measured by neutron activation analysis. We have demonstrated a consistent increase in calcium content of bone in dialysis patients treated with 1α(OH)D₃ as measured by neutron activation of the forearm compared with a group of patients treated with standard dialysate calcium only. Would you comment on these differences in your results compared with our technique using the forearm?

CATTO It is true, of course, that we did report some results a few years ago, showing that there was an increase in skeletal calcium content immediately after we started treatment with 1 alpha. I think the reason for that was that the patients in that study were specially selected because they had the greatest decrease in skeletal calcium content prior to the start of therapy. And I think the results that we showed on that occasion are similar to the changes that are shown here, in that we can prevent continuing skeletal demineralisation. The problem seems to be that we are unable to show over a prolonged period of time a sustained increase in skeletal calcium. In some patients we can demonstrate a short-lived increase, which may well represent the subperiosteal erosion healing. However we have so far been unable to show a continuing increase in the skeletal calcium.

MARSH (London) Have you had any difficulty in maintaining a satisfactory dose of one alpha or 1,25 dihydroxy D₃ following your initial treatment. Following production of biochemical and radiological remission with one alpha we have had to reduce the maintenance dose drastically because of hypercalcemia, which persists and is associated with an increase in serum PTH, which in initial treatment had returned to normal.

CATTO We had exactly the same problem. People have suggested of course that perhaps one alpha may have a direct inhibitory effect upon the secretion of PTH. Our solution has been to perform parathyroidectomy at an early stage so that we could maintain reasonable dose schedules with one alpha or one-twenty five.

WILMINK (Amsterdam) Did you supply to your patients, in addition to the diet, in the period you did not give vit. D analogues extra calcium by oral calcium supplementation?

CATTO We have been giving calcium carbonate to increase the amount of calcium in the diet, approximately 1 or 1.5 grams per day of elemental calcium.