OSTEOPENIA DURING LONG-TERM HAEMODIALYSIS: RESPONSE TO VITAMIN D₃ ANALOGUES

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Introduction

Prolonged haemodialysis is accompanied by a marked and progressive reduction in bone mass [1,2]. This osteopenia develops first in the early stages of chronic renal failure [3] but accelerates during long-term haemodialysis [2]. The exact aetiology of skeletal demineralisation in end-stage renal failure is unclear but it is likely that secondary hyperparathyroidism [4] is the major cause with vitamin D resistance, systemic acidosis and other factors such as heparin [5] playing subsidiary roles.

Clinical features of osteopenia such as bone pain and spontaneous fractures, often accompanied by serious skeletal deformities, are a source of considerable morbidity amongst maintenance haemodialysis patients [2]. Despite the significant advances made in the effective treatment of other features of renal osteodystrophy, treatment of established osteopenia remains imperfect and the extent to which therapy with vitamin D₃ analogues can reverse progressive skeletal demineralisation has not been established [6]. Short term treatment with 1α(OH)D₃ or 1,25(OH)₂D₃ has been reported to increase skeletal mass in haemodialysis patients [7] but this beneficial effect has not been sustained in the few long-term studies that have been reported [8,9].

The confusion over the beneficial effect of 1α and 1,25(OH)₂D₃ on skeletal mass is at least partly due to the lack of a single diagnostic technique that can accurately chart small changes in skeletal calcium content. We report here the results of long-term studies of 1α(OHD)₃, 1,25(OH)₂D₃ and another dihydroxylated D₃ metabolite, 24,25(OH)₂D₃ on skeletal mass in a group of maintenance haemodialysis patients.

Patients and methods

A total of 34 patients aged 22–61 years (mean 39.4 ± SD 11.3) on maintenance haemodialysis for 3–119 months (42.3 ± 35.4) were studied. Ten patients received
treatment with 1α-hydroxycholecalciferol (1αOHD₃) 0.5–2µg/day for 6–36 months (21.3 ± 11.2). The starting dose was 2µg/day and this was later reduced to the maximum dose compatible with normocalcaemia. Twelve patients were given 1,25 dihydroxycholecalciferol (1,25(OH)₂D₃) 0.25–1µg daily for 3–30 months (12.8 ± 8.2). The starting dose was 1µg/day and again the dose was reduced as necessary to the maximum dose compatible with normocalcaemia. Eleven patients were treated with 24,25 dihydroxycholecalciferol (24,25(OH)₂D₃) in a fixed dose of 2µg/day for 6–18 months (9.7 ± 3.3). This dose of 24,25(OH)₂D₃ has been shown to produce serum concentrations of 24,25(OH)₂D₃ above or within the normal range in maintenance haemodialysis patients. All patients received sufficient aluminium hydroxide to keep predialysis serum phosphate concentration less than 2.0mmol/L.

The following investigations were carried out in all patients. Serum calcium (Ca), phosphate (PO₄), albumin, alkaline phosphatase (AP) and parathyroid hormone (PTH) concentrations were estimated at 6 weekly intervals before and during treatment. Ca, PO₄, albumin and AP were estimated by the Department of Chemical Pathology, University of Aberdeen, using a SMAC Autoanalyser (Technicon UK Ltd). PTH assays were performed at the Middlesex Hospital, London, using two completely different assays. For the early studies of 1αOHD₃ treatment a non-region-specific anti-bovine PTH assay system was used [10]. In patients treated with 1,25(OH)₂D₃ and 24,25(OH)₂D₃ a newly described human amino-terminal specific immunoradiometric assay was used [11].

Progress of demineralisation was assessed by full thickness iliac crest bone biopsies obtained before and at six monthly intervals during treatment and also by six monthly radiological skeletal surveys. Changes in skeletal Ca were monitored by partial neutron activation analysis (NAA) of a hand. This technique has been described in detail elsewhere [12] and relies on the conversion of naturally occurring ⁴⁸Ca to unstable ⁴⁹Ca which is a γ emitter. Measurement of the γ emission as ⁴⁹Ca decays gives a crude estimate of changes in the Ca content of a hand.

Results

Changes in serum Ca, PO₄ and AP concentrations were not significantly different in the patients treated with 1,25(OH)₂D₃ and 1αOHD₃ and the results from these groups have therefore been pooled. Following treatment with 1αOHD₃ or 1,25 (OH)₂D₃ serum Ca rose significantly and serum PO₄ was unchanged. Serum AP fell significantly in the early months of treatment but began to rise again after 18 months. Mean serum PTH fell significantly in both the 1αOHD₃ and 1,25(OH)₂D₃ treated patients and remained low though a late rise was seen in the 1,25(OH)₂D₃ treated group due to a single patient in whom N-PTH rose after one year on treatment having initially fallen to normal within 3 months of starting treatment.

Following treatment with 24,25(OH)₂D₃ serum Ca was unchanged and mean serum AP rose though not significantly. There was a transient though significant fall in mean serum PO₄ during the early months of treatment though this had returned to baseline by one year. Mean serum N-PTH was unchanged following 24,25(OH)₂D₃ treatment.

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Figure 1. Neutron activation analysis response to 1αOHD₃ and 1,25(OH)₂D₃. Figures in brackets refer to number of patients at each point. p values refer to difference of the slope of the linear regression line from zero.

Figure 2. Neutron activation analysis - response to 24,25(OH)₂D₃. Figures in brackets refer to number of patients at each point. p values refer to difference of the slope of the linear regression line from zero.
The pattern of histological type of renal osteodystrophy was similar in all the treatment groups with around 24% of patients having 'pure' osteomalacia, 45% features of osteomalacia and secondary hyperparathyroidism, 8% osteitis fibrosa alone and 10% osteopenia alone. Following treatment with 1αOHD₃ or 1,25(OH)₂D₃ bone histology improved in 77.3% of patients, worsened in 9.1% (with the development of mild osteomalacic changes) and was unchanged in 13.6%. In the 24,25(OH)₂D₃ treated group bone histology improved in 10%, worsened in 60% and was unchanged in 30%. It was notable, however, that the major improvements noted in the 1αOHD₃/1,25(OH)₂D₃ treated patients were in patients having combined osteomalacia and secondary hyperparathyroidism. The incidence of 'pure' osteomalacia was similar before and after treatment with 1αOHD₃/1,25(OH)₂D₃ though it was much less severe following such treatment.

Before treatment, bone mass as assessed by partial NAA was declining in all patients. Following treatment with 1αOHD₃ or 1,25(OH)₂D₃ the fall in skeletal Ca content was arrested though not reversed. At 18–24 months however, bone mass had begun to decline again though more slowly than before treatment (Figure 1). In contrast, treatment with 24,25(OH)₂D₃ had no effect on the rate of decline in bone mass assessed by partial NAA (Figure 2).

Conclusions

These studies have confirmed the established role of 1αOHD₃ in controlling biochemical and histological features of renal osteodystrophy though treatment with 24,25(OH)₂D₃ alone was ineffective. Treatment with 1αOHD₃ or 1,25(OH)₂D₃ slowed the rate of skeletal demineralisation in the short term although there was a tendency for bone mass to decline at a somewhat slower rate after 1–2 years of treatment. Such treatment did not, however, restore bone mass to osteopenic bone. In contrast, treatment with 24,25(OH)₂D₃ alone had no effect on decreasing the rate of skeletal demineralisation.

Acknowledgment

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References

1 Ellis HA, Peart KM. Nephron 1971; 8: 402
2 Parfitt AM, Massry SG, Winfield AC. Clinical Orthopaedics and Related Research 1972; 87: 287
4 Massry SG, Ritz E. Arch Intern Med 1978; 138: 853
6 Anonymous. Lancet 1979; ii: 1339
8 Junor BJR, Catto GRD. Clin Endocrinol 1977; 7: Suppl 131s
9 Kanis JA et al. Quart J Med N S XLIll 1979; 190: 289
12 Catto GRD, McIntosh JAR, MacLeod M. Physics in Medicine and Biology 1973; 18: 508

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Open Discussion

WILL (Leeds, UK) Could you tell us the evidence on skeletal demineralisation by neutron activation analysis in an equivalent control group? What I had in mind is that drawing lines through scattered data points and predicting slopes is hazardous, and you could argue, for example, that your last graph showed an early demineralisation which was actually reaching a plateau after perhaps 2 years.

MUIRHEAD The amount of radiation that is involved, although not substantial, is sufficient to mean that there would be ethical problems about using this technique on normal subjects so I know of no control data on this. However, there are clear differences in the two treatment groups, so in a sense patients who were treated with 24, 25(OH)\(_2\)D\(_3\) act as a control group for the patients given 1αOHD\(_3\) or 1,25(OH)\(_2\)D\(_3\).

WILL I'm sorry to pursue you on the point but I did not mean control subjects — I meant control dialysis patients. Is your last statement statistically sound?

MUIRHEAD I obviously misunderstood you. We do have other dialysis patients who have not received treatment with vitamin D analogues and the pattern of demineralisation is similar to that which I have shown.

SWENSON (Stanford, California) It seems to me that you've shown us that two vitamin D products elevated the serum calcium and improved the bone quality. And a third vitamin D did not elevate the serum calcium and there was no change in the bone histology. Is this simply a dosage phenomenon?

MUIRHEAD I'm not sure whether it is a dosage phenomenon or not. Obviously, we have not explored the effect of increasing dosage of 24,25(OH)\(_2\)D\(_3\). What we were trying to do with 24,25 was to produce physiological concentrations of the metabolite by giving a daily dose that approximated to the endogenous production. These patients did achieve 24,25(OH)\(_2\)D\(_3\) concentrations within the physiological range. Obviously, if we had used pharmacological doses of 24,25(OH)\(_2\)D\(_3\) we might have observed a different response, but we didn't do this.

FOURNIER (Amiens) I have been very interested by your data showing that 2µg per day of 24,25(OH)\(_2\)D\(_3\) has no efficacy on hyperparathyroidism and osteitis fibrosa. It is unfortunate that you don't have the plasma levels of 24,25 (OH)\(_2\)D\(_3\) because they are unpredictable in uraemic patients, being either low, normal or even high as we reported last year. In patients with high levels already you cannot expect that 2µg will give good results. However, it may be good to give 24,25(OH)\(_2\)D\(_3\) to those who have low 24,25 which does not increase by 1 alpha and 25OHD\(_3\) administration since in our experience, administration of those vitamin D metabolites to those cases was not effective in curing bone hyper-resorption.

MUIRHEAD I have got the plasma data and obviously in a presentation of this
length it's impossible to include everything. In all of the patients in whom we measured 24,25(OH)₂D₃ before treatment, the levels were almost undetectable by the assay that was used. As far as we know all of the patients who received 24,25(OH)₂D₃ had low plasma 24,25(OH)₂D₃ before treatment. As I have just said, these levels were within the physiological range after treatment.

FOURNIER Our data which was presented last year suggested, however, that in order to improve osteitis fibrosa you should increase plasma levels of 24,25(OH)₂D₃ above normal – not within the normal range, since improvement of bone hyperresorption was seen only in those who have had abnormally high plasma levels of 24,25(OH)₂D₃.

MUIRHEAD Well, perhaps we should have given more, though this was not the main point of our studies.

SCHULZ (Bamberg) Have you measured the osteoid volume before and after therapy?

MUIRHEAD We are in the process of analysing all the biopsies quantitatively, but I don't yet have the data on osteoid volume in these patients.

SCHULZ Do you have experience with sodium fluoride in the treatment of osteopenia?

MUIRHEAD No.

ZINGRAFF (Paris) Did you exclude aluminium intoxicated patients from your study because osteomalacia in these patients is known not to respond very well to vitamin D analogues?

MUIRHEAD As far as we know, none of the patients that we've studied were suffering from aluminium intoxication.

HEAF (Copenhagen) I noticed your alkaline phosphatase and PTH results showed large standard deviations and I think part of your problem is that those parameters are not normally distributed. If you used a logarithmic transformation before analysing your data you would achieve higher significance rates for those curves which are otherwise quite impressive.

MUIRHEAD I did log-transform the data and it didn't make very much difference to the overall statistical significance of the results.

HEAF Should all dialysis patients now receive active vitamin D metabolites?

MUIRHEAD I don't think we're in a position to answer that yet and my feeling would be 'no'. We need to study this matter more fully before we can make any statement on that.