THE EFFICACY OF VARIOUS TREATMENT MODALITIES ON ALUMINIUM ASSOCIATED BONE DISEASE

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Summary

We have studied the effects of desferrioxamine (DFO) or successful renal transplantation on eight patients identified as having aluminium associated bone disease. All patients showed dramatic subjective improvement in their bone pain and/or fractures. All histological parameters studied improved, with the more normal bone being found in the transplanted patients. Bone aluminium fell by at least 50 per cent. Biochemically, increased bone activity was indicated by a rising alkaline phosphatase. This was particularly marked in the DFO treated group who tended to show the development of hyperparathyroidism.

Introduction

Aluminium associated bone disease (AABD) in its fully developed state is characterised by severe bone pain, spontaneous non-healing fractures, lack of radiological, biochemical and histological evidence of hyperparathyroidism and a severe atypical form of osteomalacia with a tendency to hypercalcaemia and resistance to vitamin D therapy [1]. A number of studies [2, 3] have confirmed the presence of aluminium at the junction of mineralised-bone (MB) and osteoid. The pre-symptomatic stage can be recognised in people exposed to high dialysate aluminium levels by a simple histochemical technique [3, 4] even when there is a total lack of renal osteodystrophy radiologically.

In trying to prevent this form of osteodystrophy, emphasis has been placed on minimising the accumulation of aluminium in the body by adequate water treatment with reverse osmosis or deionisation [5], as well as restricting the amount of aluminium containing phosphate binding drugs ingested. This is not yet universal practice.

Successful treatment of AABD and dialysis dementia (the other clinical condition attributed to aluminium accumulation in cortical grey matter [1]) has been reported only anecdotally following successful renal transplantation [6],

195
although therapy with desferrioxamine (DFO) has been shown to decrease serum aluminium values [7].

We investigated the changes in bone aluminium content and bone histology in patients with known AABD. The effect of continued haemodialysis against untreated water in conjunction with DFO administration was compared with a similar number of patients who received a successful renal transplant.

Patients and methods

Eight patients were studied. The patients receiving a renal transplant (n = 4) were generally younger than those treated with DFO (\(\bar{X} = 34\) years versus 46 years). The DFO group (n = 4) had generally been on dialysis longer (\(\bar{X} = 4.4\) years versus 2.7 years). All patients however were markedly symptomatic with severe bone pain and many had fractures. Four patients were wheel-chair bound (three DFO treated). All patients fitted into the clinical, biochemical and histological profile for AABD.

Trans-iliac bone biopsies were performed prior to DFO or transplantation and repeated six months post-therapy and processed for aluminium assay by atomic absorption spectrophotometry and for histology as previously described [8]. All patients received tetracycline markers 24 and three days before biopsy so that bone apposition rate could be evaluated.

Histomorphometric measurements were carried out using the programme of Dunstan and Evans [9] employing a Hewlett-Packard 9874A digitiser interfaced to a Hewlett-Packard 9825A desk top computer. The areas for total bone (% section area), osteoid (% total bone), osteoid with active osteoblasts (% osteoid surface), osteoclasts (per \(\text{mm}^2\) of section area) were obtained. Aluminium present at the junction of mineralised bone (MB) and osteoid was measured directly by tracing the stained area and expressed as a percentage of total bone surface. The coefficient of variation in all parameters was less than 10 per cent.

Bone apposition rate was calculated for active seams and expressed in \(\mu\text{m}/\text{d}\). It was obtained by dividing the distance between tetracycline markers by the number of days apart they were taken.

Desferrioxamine (DFO) was administered intravenously at a dosage of 1 g post-dialysis, three times per week. Post-dialysis administration caused at least a 50 per cent increase in plasma aluminium concentration and an increase of 8–10 fold in dialysate aluminium, compared to pre-dialysis administration.

Results

Pre-therapy, atypical osteomalacia was present in all patients (osteoid lamellae under polarised light, range 5–14, N: < 4). Dramatic symptomatic improvement occurred with both DFO or transplantation; fractures healed, crutches and wheel-chairs were discarded and the ability to climb stairs and arise from the squatting position with ease was most dramatic.

Biochemically, following commencement of both forms of therapy, there was a dramatic increase in alkaline phosphatase. In the DFO group, this was associated with a marked increase in circulating immunoreactive PTH and lead to the intro-
duction of dihydroxy-vitamin D₃ to control the development of hyperparathyroidism, once the hypercalcaemia had abated (see Figure 1).

Figure 2 shows the trend towards normal of the various bone values evaluated. The most significant difference between the two groups was the significantly greater osteoclast count in the DFO group (p < 0.05) and the higher percentage of aluminium still discernible at the bone-osteoid junction (p < 0.05).

Pre-therapy, bone apposition rate could not be evaluated because of lack of separation of tetracycline uptake or 'smearing' over poorly mineralised bone [4]. Post-therapy, bone apposition rate was 2.7 ± 0.8µm/d in the DFO group and 1.6 ± 0.4µm/d in the transplant group (control: 1.0 ± 0.2SD).

Total bone aluminium decreased from 340 ± 88µg/g (SD) (range 220–530µg/g) pre-treatment to 125 ± 68µg/g (range 40–150µg/g) in the DFO group and 70 ± 23µg/g (range 35–87µg/g) in the transplant group (control: 24 ± 8µg/g).

Aluminium was identifiable within the bone matrix, histochemically post-therapy, compared to pre-treatment when it was only discernible at the bone osteoid junction (Figure 3).
Figure 2. Histomorphometric changes in the patients treated with dialysis and DFO, and those receiving a renal transplant
Figure 3. Aurine tricarboxylic acid stain with light green and orange G counterstain in a pre- and post-DFO treated individual. (a) Pre-transplant, aluminium is present at MB/osteoid junction, and (b) within bone matrix. Also note the reduced amount of osteoid. (Magnification × 100)
Discussion

All eight patients identified as having AABD showed dramatic subjective and objective improvement following either DFO or successful renal transplantation. The transplanted group showed greater return to normal of their bone histology parameters with total bone reaching the lower range of control values, more osteoid with osteoblastic activity, lesser counts of osteoclasts and greater bone apposition rate, i.e. improved mineralisation. Furthermore the total amount of aluminium in their bone samples tended to be less, although this failed to reach statistical significance.

One possible explanation for the greater improvement in the transplant group could be that they were generally a younger population and had been on dialysis a shorter period. However there was no difference in the histological parameters between the DFO and transplant group initially. A more appropriate explanation would be that the latter were able to excrete greater amounts of tissue accumulated aluminium in conjunction with improved physiological vitamin D concentrations.

The defective mineralisation of osteoid in AABD is probably due to binding of aluminium to mineralisation 'nuclei' at the calcification fronts of bone forming units and inhibition of bone phosphatases resulting in non-elevation of alkaline phosphatase and hypercalcaemia as a result of leaving released bone calcium in the circulation [10].

Eradication of aluminium from the bone forming units would then reverse these biochemical abnormalities as was demonstrated clearly by our patient (Figure 1). The increased alkaline phosphatase reflects an increase in bone formation or in mineralisation, or both, confirmed by the histology.

DFO is a well known chelating agent, previously thought to be specific for iron overload. It is relatively dialysable (mol. wt. ~ 500) and causes significant increases in dialysate aluminium values by mobilisation of tissue aluminium, thus increasing the effective concentration gradient between plasma and dialysate [11]. It seems therefore an effective treatment modality in those patients identified as having AABD who cannot be transplanted. Further long term studies are needed to see whether even greater improvement in bone histology occurs, although the development pari passu of hyperparathyroidism should be carefully monitored.

Treatment of dialysate water is paramount in all dialysis centres. However non-aluminium containing phosphate binders, e.g. calcium carbonate, should also be used to minimise this long term dialysis-associated disease.

Acknowledgments

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References

Open Discussion

JACOBS (Paris) A rapid calculation shows that over the six month period that you have described the patients will have received about 75 grams of Desferrioxamine. The molecular weight of Desferrioxamine being about 800 one might speculate some accumulation of this drug. Have you observed any side effects, acute or chronic, that may be due to the drug, and secondly can you tell us about the dialysis techniques that were used in your patients?

IHLE We have not observed any complications with prolonged Desferrioxamine treatment. We were aware of this potential problem initially but we weighed it against the continuing symptomatic disability of the patients. Therefore we went ahead with these four patients on dialysis treatment giving them Desferrioxamine. These four patients were not transplanted because of high circulating lymphocytoxic antibodies thus we had to weigh the risks against the benefits. In answer to the second question we used hollow fibre dialysers for three patients and the other patient was on peritoneal dialysis and had Desferrioxamine administered three times weekly intramuscularly.

MARUMO (Sagamihara) According to our measurement of bone using neutron activation analysis we found both the calcium magnesium and the calcium aluminium ratio decreased. In other words, aluminium and magnesium content increases with decrease of calcium in the bone. Did you find the increased magnesium in bone?

IHLE We have not measured magnesium, but the calcium aluminium ratios are diminished.

ROBINSON (Birmingham) You did not mention the subject of encephalopathy in your talk and I wondered whether you have seen encephalopathy associated with these patients. I ask this because although we had been free from this problem in Birmingham until recent years we suddenly began to get an outbreak of fracturing osteodystrophy which was, however, clinically less of a problem to the patients than the development of encephalopathy. My experience of transplanting these patients with the preliminary signs of encephalopathy was disastrous, they rapidly deteriorated mentally.
The bone disease has shown a remarkable clinical and histological response to better water treatment alone. To refer to the point that Dr Jacobs raised I would agree with you, we have used Desferrioxamine in these doses for up to eighteen months in patients with encephalopathy without any suggestion of toxicity.

IHLE One of the patients who was going to be included in the study of the dialysis patients actually died of dialysis dementia concurrently with bone disease. The reason I pointed out the difference in age and dialysis time in the transplant group both being less than the other group is that probably dialysis dementia may take a lot longer to develop and the bone disease may well be an earlier type of problem related to aluminium, especially if you get very high sudden exposure to aluminium as we have now found since the Melbourne water supplies now contain an extremely high aluminium content.

DAVISON (Leeds) I was interested in your comment that the bone disease gets better after transplantation. In the patients we have seen with dementia we have been concerned because after transplantation, as in Dr Robinson's experience, they get very much worse. Our thoughts, at the time, were that it was due to aluminium coming out of the bone from an effect of steroids. I wondered if you have looked at any of your bone biopsies after transplantation by the aluminium staining methods that you described to see whether in fact it is the same or less.

IHLE That last slide where I showed the aluminium in the bone matrix was from one of the transplanted patients. All I can say is in fact the bone parameters looked, after six months of good renal transplant function, much better than in the patients still on dialysis.