

TREATMENT OF FRACTURING RENAL OSTEODYSTROPHY BY DESFERRIOXAMINE

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Summary

Aluminium removal by desferrioxamine chelation has been demonstrated in three long-term haemodialysis patients with dialysis encephalopathy and fracturing renal osteodystrophy. Aluminium concentrations in serum and in both bone marrow and bone trabeculae, determined separately in transiliac biopsy specimens, fell significantly over the treatment period. Bone aluminium removal was confirmed by specific histochemical staining. In two patients osteomalacia disappeared, and in two patients osteitis fibrosa emerged but improved in one following vitamin D therapy. We conclude that desferrioxamine is capable of mobilising aluminium from bone and that the calcification defect in fracturing renal osteodystrophy may be overcome.

Introduction

There is strong evidence that aluminium accumulation from dialysate [1,2] and aluminium-containing oral phosphate binders [3] is the cause of a variety of toxic symptoms among patients undergoing chronic haemodialysis. These include dialysis encephalopathy [4], an osteomalacic bone disease known as fracturing dialysis osteodystrophy [5], and a microcytic anaemia [6].

It has proved impossible to remove significant quantities of aluminium by conventional dialysis alone. However, we have shown previously that aluminium can be removed in substantial quantities by dialysis following chelation with desferrioxamine [7], and this has since been confirmed [8]. During our earlier study, a patient with advanced dialysis encephalopathy showed striking clinical improvement and we observed profound changes in the biochemical and histological characteristics of his bone disease. We have now carried out further studies on this patient and two additional patients to investigate the possibility of aluminium removal from bone, using a new chemical technique to quantify the aluminium content of marrow and trabeculae separately. We have also studied aluminium distribution within the bone using histological techniques.

Patients

Chelation therapy was undertaken primarily for symptoms of dialysis encephalopathy in all three cases. The patients, GH, GO and WA (males aged 37, 26 and 67 years respectively) had been on chronic haemodialysis for nine, six and 15 years respectively. Renal failure was due to chronic pyelonephritis in the first two patients and probable chronic glomerulonephritis in the third. Patient GH had taken no oral aluminium and had dialysed with untreated tap water with high aluminium concentrations (100–500 µg/L) until 18 months prior to chelation therapy, when a deioniser was installed. The other two patients both ingested aluminium hydroxide regularly and dialysed without water treatment at dialysate aluminium concentrations (40–80 µg/L (GO) and 10–40 µg/L (WA).

Treatment

The patients underwent chelation therapy with desferrioxamine (Desferal, Ciba) as previously described [7]. Desferal (DFO), 4 to 6g in 500ml N saline, was infused into the arterial line of the dialyser (1m² flat plate, single pass) once weekly during the first two hours of dialysis. The blood and dialysate flow rates were 200 and 500ml/min, respectively. The dialysate water supply was treated with a mixed bed deioniser (Elga R200). The aluminium content of the deionised water was below 5 µg/L and the final aluminium concentration of the dialysate was below 15 µg/L. During DFO therapy, dialysis was reduced to four hours thrice weekly and prophylactic anti-epileptic therapy including phenobarbitone, phenytoin, diazepam or clonazepam was given orally. Aluminium containing phosphate binding drugs was stopped.

Patients GH and WA were treated for single periods of 10 and five months respectively, and GO was treated for two periods, of four and 10 months, interspersed by three months without treatment (Table I).

TABLE I. Serum biochemistry and haemoglobin

Patient	Treatment period (months)	Ca mM/L	PO ₄ mM/L	AP iu/L	iPTH ng/ml	Hb g/dl
GH	10 pre DFO	2.36	2.1	127	1.0	5.2
	12 post DFO	2.05	2.7	308	13.0	7.2
	post vit D	2.30	2.9	90	5.5	6.4
GO	4 pre DFO(1)	2.30	3.3	107	2.3	6.1
	3 post DFO(1)	2.20	3.0	152	—	5.2
	10 pre DFO(2)	2.44	2.9	209	4.0	*7.8
	post DFO(2)	2.27	3.2	186	6.0	10.4
WA	5 pre DFO	2.55	1.9	285	14.0	7.0
	post DFO	2.55	3.0	201	—	8.2

iPTH = Immunoreactive parathormone, by courtesy of Dr GA Lumb, Department of Medicine, Manchester Royal Infirmary. Normal range 0.2–0.8ng/ml.

*Transfused 2 units, two months previously.

Methods

Serum, dialysate and bone solutions were analysed for aluminium by atomic absorption spectrometry using graphite furnace atomisation (Perkin Elmer HGA-500 furnace). Aluminium removal during dialysis sessions was determined from the concentration differences between the dialyser input and output, sampled simultaneously at 30 minute intervals during dialysis.

Serial transiliac bone biopsy specimens were obtained by the Bordier technique, fixed and then further dehydrated in absolute ethanol, and double embedded in low viscosity nitrocellulose and wax [9]. For aluminium analysis, cancellous bone was pared from the blocks, washed free of embedding material, and vacuum dried to constant weight. The bone samples were ashed in platinum crucibles using an inductively excited low pressure oxygen plasma to remove the organic components of the marrow. The inorganic residue of the marrow was washed from the trabecular matrix and dissolved in nitric acid (fraction 1). The remaining trabecular portion of the bone was dried under vacuum, weighed, and also dissolved in nitric acid (fraction 2). Aluminium concentrations in fractions 1 and 2 were used to calculate the dry-weight aluminium concentrations in marrow and trabeculae, respectively.

Bone histology

Oral tetracycline (1g) was given one week prior to biopsy (except WA post mortem). Labelling was assessed in uv-blue light in unstained 20 μ m undecalcified sections. Osteoid was delineated in undecalcified 8 μ m sections stained with Von Kossa and toluidine blue. Aluminium staining in both mineralised bone and bone marrow was carried out using a solachrome technique (J Ball and J Denton, unpublished). The diagnosis of osteomalacia required absent or grossly defective labelling plus excessive osteoid with (Grade 2) or without (Grade 1) abnormally thick seams. Osteitis fibrosa was graded 0–3 by inspection.

Results

Blood biochemistry data are given in Table I. Patient GH was treated with vitamin D (1.5 μ g/d) for 12 months after DFO therapy. During DFO, both GH and GO showed higher values of alkaline phosphatase, with maxima 490 and 269iu/L, respectively. The serum PTH rose in both patients, the value falling in GH during vitamin D therapy. There was a significant rise in haemoglobin during DFO treatment in all three patients, especially GO, who had previously required repeated transfusion to maintain haemoglobin between 5–6g/dl.

Bone and serum aluminium concentrations fell considerably over the treatment periods (Table II). There was a striking reduction in both marrow and trabecular aluminium, confirmed by solachrome staining. The amounts of aluminium removed by dialysis from patients GH and WA were 600 and 400mg, respectively, and from patient GO, 50 and 300mg during the first and second periods, respectively.

Prior to chelation therapy, all patients exhibited severe signs and symptoms

TABLE II. Serum and bone aluminium and bone histology

Patient		ALUMINIUM ANALYSIS				Serum ($\mu\text{g/L}$)	HISTOLOGY			
		Whole	Bone ($\mu\text{g/g}$) Trab Marrow		Al staining Trab Marrow (0-4) (0-2)		OM (0-2)	OF (0-3)		
GH	pre DFO	372	527	252	140	4	2	2	0	
	post DFO	116	213	91	116	3	1	0	2	
	post vit D	101	149	57	58	3	0	0	2	
GO	pre DFO	360	245	488	76	3	2	2	0	
	post DFO	210	192	225	80	3	2	2	1	
	post DFO	54	55	53	43	2	2	0	2	
WA	pre DFO	163	242	110	167	3	2	1	2	
	post DFO*	51	53	50	140	1	1	0	2	

OM = osteomalacia; OF = osteitis fibrosa; * post mortem

of dialysis encephalopathy with speech disturbance, myoclonic jerks and convulsions, and were admitted for hospital maintenance dialysis. Patient GH had gross proximal myopathy with little bone pain. Bone X-rays showed pseudo-fractures in the pubic rami together with rib fractures. A similar picture had been present for the previous four years during which time repeated attempts at treatment with vitamin D had been abandoned because of uncontrolled hypercalcaemia. After DFO, GH showed a moderate improvement in his myopathy but there was a generalised aching in his bones and hand X-rays showed sub-periosteal erosions. During subsequent vitamin D therapy, hypercalcaemia did not occur and he became pain free and regained full muscle power. Currently (12 months later) he remains well and fully ambulant.

At the onset of DFO therapy, patient GO complained of generalised bone pain, showed signs of proximal myopathy and a peripheral sensori-motor neuropathy, and there were pseudo fractures of the pubic rami. During DFO, he regained full independence and his bone pain and proximal myopathy resolved. Patient WA also suffered bone pain, particularly in the wrists and ankles, and there was mild proximal myopathy. His clinical course on DFO was complicated by the effects of ageing, arteriosclerosis, hypertension and problems with vascular access. Despite removing considerable quantities of aluminium, there was only moderate improvement in his symptoms and he died during the fifth month of treatment following myocardial infarction.

Discussion

In all three cases, substantial quantities of aluminium were removed by dialysis during chelation therapy with DFO. Quantitative analysis showed considerable reductions of aluminium in both bone marrow and bone trabeculae, which contrasts with a recent report [10] in which no aluminium removal from bone was found in two patients treated with DFO.

Histologically, the bone in our patients became more active after DFO. The osteomalacia was corrected in two of the cases and osteitis fibrosa became apparent in the two cases where it was absent before treatment. The resolution of the calcification defect might be due to removal of aluminium from sites in cells and/or extracellular matrix, where it might act by blocking the calcium transport system. This would rationalise the improvement shown by GH during vitamin D therapy subsequent to DFO. Removal of aluminium from the bone marrow might also be responsible for the increase in haemoglobin concentration.

The cause of the hyperparathyroid changes is not clear. Neither a consistent rise in plasma phosphate nor overt hypocalcaemia was seen. It has been reported that aluminium accumulates in the parathyroid glands [11], and it is possible that removal from this site was the cause of the changes seen.

In conclusion, these studies confirm that desferrioxamine is capable of mobilising aluminium from bone, and enables the removal of aluminium from the patient by dialysis. This treatment may rectify the calcification defect present in fracturing renal osteodystrophy.

Acknowledgment

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Open Discussion

TORRENTE (Madrid) What are the iron and ferritin values in your patients?

ACKRILL The serum iron does not seem to change very much, it is quite variable. There were two distinct differences with serum ferritin, in the first patient the values remained very high and have done throughout, and there was an association between that and the haemoglobin. Whereas in the second patient, where there was a dramatic rise in haemoglobin, there was a very marked fall in ferritin, which is currently very low and he is about to receive some iron. All three have had oral iron.