Bone response in patients with aluminium-related osteomalacia after desferrioxamine therapy and adequate water treatment

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RESUMEN

Osteomalacia inducida por aluminio: respuesta ósea tras la utilización de desferrioxamina y adecuados tratamientos del agua.
La utilización de ósmosis inversa y la deionización ha traído como consecuencia una reducción de la incidencia de enfermedad ósea inducida por aluminio. Sin embargo, en muchos casos a pesar de adecuados tratamientos del agua y a la utilización de desferrioxamina dicha patología ha persistido, lo que podría ser parcialmente explicado por las variaciones en la producción de parathormona y por fallos intermitentes del tratamiento de agua.

SUMMARY

Bone response in patients with aluminium-related osteomalacia after desferrioxamine therapy and adequate water treatment.
The use of deionisation and reverse osmosis has generally reduced the incidence of aluminium bone disease; however, it has persisted in some patients despite apparently adequate water treatment and desferrioxamine therapy. This failure might be due to several factors including different parathyroid hormone status and intermittent failures of water treatment units.

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Introduction

The use of techniques such as deionisation and reverse osmosis has greatly reduced the frequency with which the dialysis water has been associated with aluminium toxicity. Thus, aluminium bone disease is now rarely encountered in Newcastle [1] where it was first described although it has persisted in some patients in other centres [2, 3] despite apparently adequate water treatment. This apparent failure of water treatment to permit the healing of aluminium bone disease could be due to differences in parathyroid status between patients [2], to intermittent failure of reverse osmosis units or to the effects of aluminium absorbed from the gastrointestinal tract. These factors could also be responsible for the apparent failure of desferrioxamine (DFO) therapy to heal aluminium bone disease in some cases.

In this paper we review some of the published data on treatment of aluminium bone disease with DFO and water purification and describe some of our own recent findings.

Desferrioxamine therapy

Rationale for use of DFO

Desferrioxamine chelates iron to form ferrioxamine and is thought to have a similar action on aluminium to form aluminoxamine [4]. Most of the aluminium in serum is protein-bound and as such up to 90 % is not ultrafilterable during dialysis. By chelating aluminium from tissue and in serum DFO can render up to 95 % of aluminium in serum ultrafilterable. During treatment serum aluminium concentrations may rise to alarmingly high levels (up to 1000 µg/l) although in most cases this does not appear to be associated with further toxic effects. Thus, DFO therapy has been accompanied by reversal of the dialysis encephalopathy syndrome, relief of proximal myopathy and improvement in aluminium bone disease and anaemia [5].

Changes in bone histology

Previous studies of DFO therapy (3-17 months) [6, 7] have shown variable effects on bone from patients with excessive accumulation of aluminium: in most cases there is a reduction in bone aluminium concentration [6] and in aluminium staining along the osteoid/calcified bone interface with a re-emergence of secondary hyperparathyroidism [6, 7] i.e. increased bone resorption and new bone formation; in some cases there is little change in Al staining and osteoclastic resorption remains suppressed [7]. This variation in response may be partly explained by differences in the type and severity of aluminium toxicity: For example, 3 of Ott's 10 patients [7] had normal osteoid volumes and normal or minimally increased osteoid surfaces indicating that they had very mild bone disease before therapy began. Indeed, in 5 of their cases aluminium was present along less than 36 % of the total trabecular surface.

We have treated 5 patients with weekly infusions of 6 g DFO for 5-8 months. All had aluminium-related osteomalacia i.e. increased extent (osteoid surface > 60 %) and thickness of osteoid seams (> 4 birefringent lamellae seen using polarising microscopy) with extensive aluminium staining along more than 65 % of the osteoid/calcified matrix interface. Specimen processing and histomorphometric techniques have been described previously [8]. Changes in bone histomorphometry are listed in table I. Aluminium staining decreased significantly in 4 of the patients although in one of these

Table I. Bone histomorphometric and biochemical values before and after DFO therapy

Patient	Age	Sex	Al staining (% osteoid surface)		Osteoid Volume (% cancellous bone)		Resorption Surface (% total surface)		Number of osteoclasts (per mm²)		Parathyroid Hormone (ng/l)	
			Before	After	Before	After	Before	After	Before	After	Before	After
1	29	F	94.3	54.9	14.6	5.2	2.6	17.7	0.30	2.14	590	590
2	29	M	66.9	16.2	6.1	5.6	17.9	16.9	1.83	0.96	2800	2600
3	53	M	79.0	33.7	21.6	9.9	3.2	32.4	0.50	6.50	510	600
4	49	F	72.9	1.6	12.1	9.0	7.0	29.5	1.43	3.40	800	2600
5	39	F	76.8	68.4	8.5	9.0	1.7	5.9	0.24	0.24	480	430
Normal * Range			0		3.8		7.3		0.28		UD - 600	

* Values were obtained from bone taken post mortem from 23 subjects who died suddenly with no evidence of bone disease.
UD = undetectable.

(No. 1) it was still present along 55 % of the osteoid. In one case (No. 4), however, aluminium staining almost completely disappeared from the surface of the bone and could not be detected within the calcified bone matrix. Aluminium staining remained virtually unchanged in patient No. 5 whose resorption surface and number of osteoclasts/mm^2 remained within the normal range. Resorption indices rose sharply in 3 patients and remained elevated in patient No. 2 who already had increased resorption and signs of recovery from aluminium toxicity before the start of DFO therapy. Thus, our findings are similar to those reported in previous studies of DFO therapy in patients with aluminium-related osteomalacia.

The increased bone resorption after DFO is likely to be due to the re-emergence of secondary hyperparathyroidism which has been observed biochemically in some patients [6, 7]. This could be partly due to chelation of aluminium from parathyroid glands. Surprisingly, parathyroid hormone (PTH) levels remained within the normal range in 2 of our patients despite pronounced rises in bone resorption.

The explanation for the failure of DFO to remove aluminium from bone or to be accompanied by increased bone resorption in some cases is not clear. It seems to be more commonly associated with "aplastic" aluminium bone disease in which osteoid seams are increased in extent but not in thickness.

Mechanism of action of DFO on bone

Two possible mechanisms could explain the reduction in bone aluminium content: chelation of aluminium from bone and from the extra-cellular matrix; and removal of aluminium-loaded calcified bone matrix by osteoclastic bone resorption. The former mechanism proposed by Ackrill and colleagues [6] is based on an apparent reduction in aluminium staining using solochrome azurine [5] and on a reduction in aluminium content measured by atomic absorption spectrophotometry. Our findings of almost complete disappearance of aluminium from the bone in 1 patient might appear to support this hypothesis. This reduction in aluminium was, however, accompanied by a pronounced increase in osteoclastic resorption and high PTH levels. The persistence of aluminium along 16-68 % of the osteoid/calcified bone interface and also extensively within calcified bone matrix in the 4 remaining patients argue against this hypothesis. We believe that most of the aluminium is removed from bone by osteoclastic resorption and that osteoblasts subsequently lay down new matrix which has a low aluminium concentration. This removal of aluminium may be assisted by the appearance of the diffuse form of calcification of thickened osteoid seams during therapy that we have described previously in this journal [9]. Once complete, this calcification would facilitate the resorption of bone by osteoclasts which rarely, if ever, resorb unmineralised matriz.

Table II. Highest recorded aluminium levels in untreated tap water in towns within a 50 km radius of Glasgow

Town	Aluminium concentration µg/l
Paisley	905
Rutherglen	920
Airdrie	1010
Coatbridge	220
Dumbarton	426
Johnstone	2980
Hamilton	925

Removal of aluminium from dialysis water

The levels of aluminium (Al) in public water supplies vary considerably from town to town (and even within towns with more than one reservoir) and from time to time as a result of the intermittent addition of aluminium salts to keep tap water clear. Table II shows the highest recorded levels of aluminium in water supplies and town within a 50 kilometre radius of Glasgow where levels are generally less than 30 µg/l. Figures 1-2 show the variation in water Al levels that occurred in 3 separate public water supplies over a 12-30 month period.

An EEC Directive (1984) has recommended that from 1st January 1986 dialysate Al levels should not exceed 30 µg/l and that this level should be reduced to 10 µg/l by 1st January 1988. Whether dialysis units in member states manage to achieve these levels remains to be seen.

Techniques for removing aluminium from water

Deionisation and reverse osmosis (RO) are the two most commonly used methods and these have largely replaced water softening techniques. Aluminium can exist in anionic, cationic and colloidal forms in solution [4]. Deionisation removes anionic and cationic forms while reverse osmosis can remove all three. However, in areas where Al levels are particularly high such as Johnstone (table II) we have found it necessary to use water softening, reverse osmosis and deionisation in series and to regularly clean the RO unit to maintain satisfactory control.

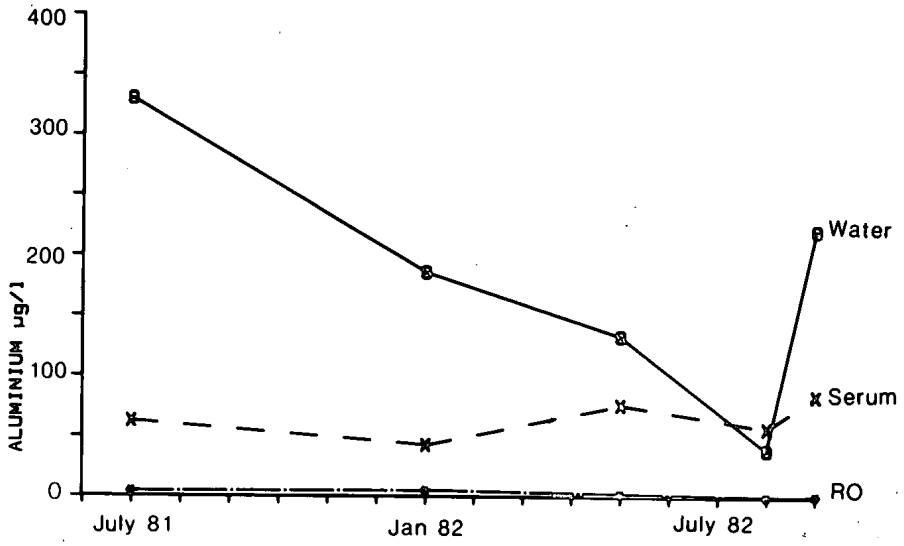

Fig. 1.—Serum Al levels remain below 100 µg/l with good RO function.

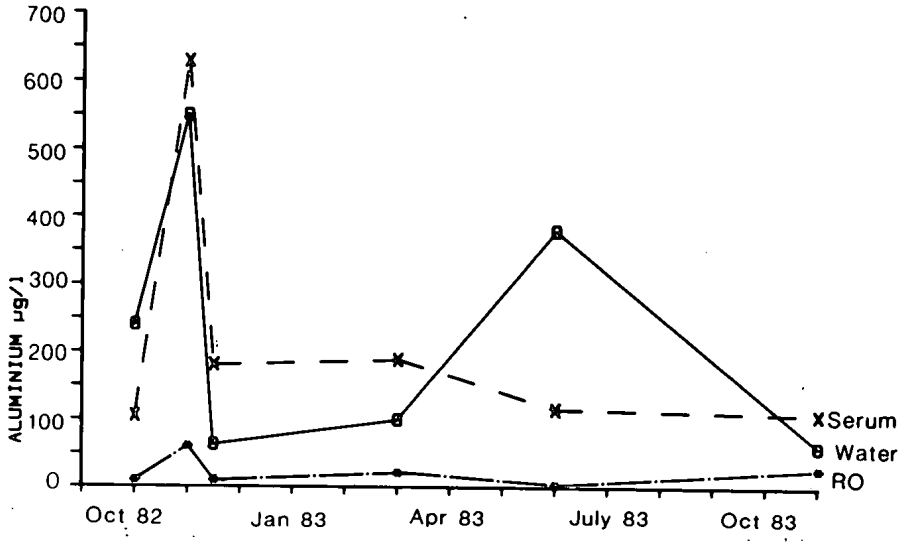

Fig. 2.—Serum Al rises sharply in November '82 despite apparently good RO function and remains around 200 µg/l until March '83.

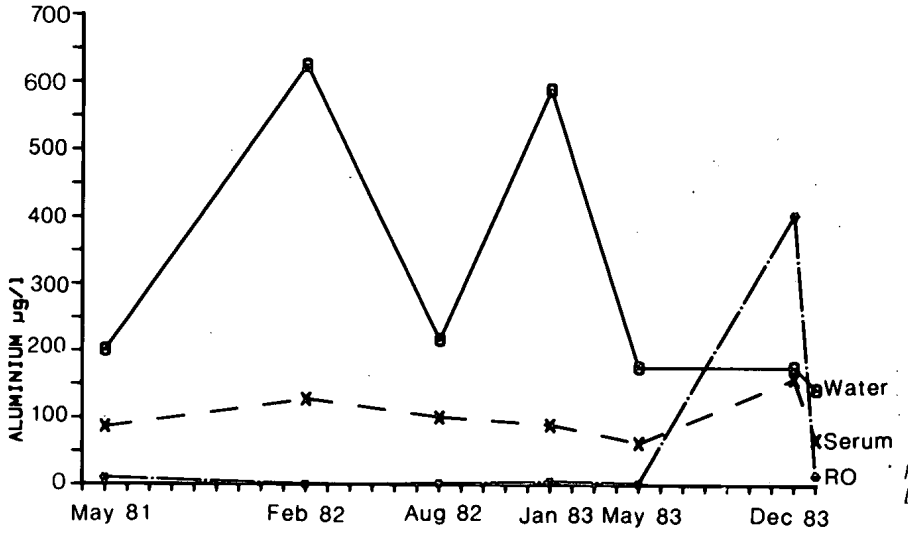

Fig. 3.—Good RO function is maintained until December '83 but failure is associated with only a small rise in serum Al concentration.

Effects of water treatment on bone histology

Since the introduction of reverse osmosis to treat dialysis water in Newcastle, Al bone disease has become a rarity [1] and a successful transplantation programme has prevented long-term consumption of phosphate binders being a cause of osteomalacia. Unfortunately, this level of success has not been achieved in all centres [2, 3]. A recent report from Edinburgh, Scotland [2], has shown that out of 7 patients who had Al-related osteomalacia before introduction of reverse osmosis units, 4 still had osteomalacia 3 years later while the remaining 3 still had some positive Al staining despite reversal of the osteomalacia. The authors suggested that the differences in the responses may have been due to differences in parathyroid gland function prior to the onset of osteomalacia. Two other possibilities, however, are that intermittent failure of the RO units may have occurred or that continued use of phosphate binders may have resulted in maintenance of the mineralisation defect.

These potential problems are illustrated in figures 1-3 which show changes in serum, untreated water and RO treated water Al levels in 3 patients. Good RO control is seen in the patient illustrated in figure 1. Despite relatively high water levels, RO levels remained 10 µg/l while serum levels were less than 100 µg/l. In the patient illustrated in figure 2 good RO control was maintained for 2 years until May '83. By December '83 the RO water level had risen to 420 µg/l and this was associated with only a modest rise in serum Al to 160 µg/l. Prompt replacement of the RO membrane resulted in a sharp fall in the water and serum levels. The third patient illustrated in figure 3 had good overall RO control but had considerable variation in serum Al levels. All 3 patients had been taking phosphate binders and while the variation in the last patient could be due to hyperabsorption of aluminium, contamination of serum samples taken in November '82 (640 µg/l) may have occurred since the RO water level reached only 60 µg/l at a time.

Failure of RO units in our experience appears to be a relatively infrequent occurrence which should be preventable by regular cleaning and occasional renewal of the RO membrane. Measurement of the serum level alone may fail to detect periods of RO failure and it is now our practice to measure RO water Al levels 5-6 times per annum.

Acknowledgements

We thank the staff of the Bone Metabolism Laboratory for technical assistance and Miss M. Habbick for typing the manuscript.

The work was partly supported by a grant to BFB from the Scottish Hospital Endowments Research Trust.

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