REVERSIBLE MICROCYTIC HYPOCHROMIC ANAEMIA IN DIALYSIS PATIENTS DUE TO ALUMINIUM INTOXICATION

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Summary

Twelve patients being treated by intermittent haemodialysis developed a severe microcytic hypochromic anaemia despite adequate iron supplements. Serum ferritin concentration was normal or high. Seven patients later developed histologically proven fracturing osteomalacia and one a fatal encephalopathy. Plasma aluminium concentration was high in all twelve patients and the source was the water used to make up dialysis fluid. Following dialysis with aluminium free dialysis fluid, plasma concentrations of aluminium fell, red cell morphology returned to normal and haemoglobin rose. We believe that in addition to causing encephalopathy and osteomalacia, aluminium causes a microcytic hypochromic anaemia. This anaemia appears to be the first manifestation of aluminium intoxication and is reversed by removing the source of aluminium.

Introduction

Aluminium intoxication is now accepted as an important cause of encephalopathy [1–3] and osteomalacia [4] in chronic haemodialysis patients. Anaemia has been suggested as a further manifestation of aluminium accumulation [5].

We describe the development of a microcytic hypochromic anaemia in a group of chronic haemodialysis patients, apparently due to aluminium intoxication and its resolution following the use of reverse osmosis treated water for dialysis.

Patients and methods

Twelve patients (8 M, 4 F) with microcytic hypochromic anaemia were studied. Their ages ranged from 23–64 years (mean 47 years) and they had been treated by intermittent haemodialysis for periods ranging from 5 to 50 months (mean 19 months). Patients had used either untreated water for dialysis in the hospital
unit or softened water for home dialysis. Prior to October 1978 South-East Scotland had not been recognised as having significant concentrations of aluminium in its water supplies, but the development of dialysis encephalopathy in one of our patients led us to analyse water, dialysis fluid and plasma aluminium concentrations on a regular basis. From February 1979, following the discovery of significant concentrations of aluminium in certain water supplies, including that of the hospital unit, treatment of water by reverse osmosis (RO) was instituted for those at risk. All patients received water soluble vitamin supplements and 320mg of oral iron as a slow release preparation daily throughout the study. A policy of non-transfusion was in operation except when severe symptoms of anaemia developed or in the event of acute blood loss. Oral aluminium hydroxide was continued throughout the study in doses adequate to control the plasma phosphate between 1.3 and 1.9mmol/L.

Haemoglobin and red cell indices were measured regularly using a Coulter-S counter. Serum ferritin was measured by the method of Addison [6]. From October 1978 aluminium concentrations were measured prospectively in plasma and water and retrospectively in stored serum samples, by flameless atomic absorption spectrophotometry (Perkin-Elmer 272 and HGA 500 graphite (furnace), using the method of Elliot et al [3].

Figures in the text show the mean and one standard deviation unless otherwise stated.

Results

Serum B₁₂ and folate concentrations were normal in all patients. No abnormal haemoglobins were detected, there was no evidence of significant haemolysis, and the concentration of lead was not elevated in water or in blood. Occult blood loss was not detected in any patient.

Water Aluminium

The concentration of aluminium in the hospital water supply fluctuated between 0.8µmol/L and 9.8µmol/L. In the supply serving the two affected home patients, concentrations were as high as 69µmol/L.

Plasma aluminium

Before RO water treatment, the mean concentration in all hospital dialysis patients (N = 45) was 8.3µmol/L (normal < 0.2µmol/L) but the highest values were in the group with microcytic hypochromic anaemia, the mean being 15.4µmol/L (range 10.5–23µmol/L).

After RO water treatment for 15 months, the mean plasma aluminium in the patients studied had fallen to 4.6µmol/L and the mean of all the hospital dialysis patients was 3.4µmol/L.
Figure 1. Changes in Hb, MCV and plasma aluminium in the 12 patients from starting intermittent haemodialysis until RO water treatment (11 – 56 months, mean 25 months) and following 15 months of RO water treatment. Each point is the mean of 3 estimations taken over a 2 months period. The normal upper and lower limits for MCV are indicated by the broken lines.
Figure 2. Development and recovery of anaemia following RO water treatment. Hatched area delineates the normal range for MCV. RO water treatment was introduced at the point indicated by the arrow. Prior to this, softened water was used for dialysate.
Figure 3. Development and recovery of anaemia in patient receiving blood transfusion, shown by arrows. The number of units of frozen red cells given on each occasion is shown beneath the arrows. The hatched area delineates the normal range for MCV. RO water treatment was introduced at the point indicated by arrow marked RO. Prior to this, untreated water was used for dialysate.
**Ferritin**

The serum ferritin in the patients studied during the development of anaemia was normal or high with a range of 120–950 µg/L, mean 464 µg/L (normal 50–267 µg/L).

Figure 1 summarises the changes in haemoglobin (Hb), mean corpuscular volume (MCV) and plasma/serum aluminium concentrations in the patients studied before and after the use of RO water. Before RO treatment all patients showed a marked fall in both Hb (mean fall 2.5 ± 0.9 g/dl) and MCV (mean fall 22.5 ± 2.39 fl) associated with a striking rise in plasma aluminium (mean rise 13 ± 2.2 µmol/L). After 15 months of RO water treatment the plasma aluminium had fallen considerably in all patients (mean fall 11.5 ± 2.1 µmol/L) with a rise in haemoglobin (mean rise 2.6 ± 1.1 g/dl) and MCV (mean rise 20 ± 2.1 fl) towards the levels recorded at the beginning of dialysis treatment. The one patient whose plasma aluminium concentration never fell below 11 µmol/L recently died from dialysis encephalopathy. Seven of the patients studied developed histologically proven fracturing osteomalacia after the development of severe anaemia. Since RO treatment there has been a marked improvement in symptoms but bone histology has not returned to normal.

The characteristic pattern of development of the anaemia is shown in Figure 2. In this patient the Hb and MCV fell steadily as the plasma aluminium concentration increased. Following introduction of dialysis with aluminium free water, the plasma aluminium fell, there was a return of normal red cell morphology and the Hb rose to its original level. This patient developed fracturing osteomalacia nine months after development of the anaemia.

Figure 3 illustrates the course of the only patient receiving regular transfusion for anaemic symptoms. Transfusion had no effect on the development of anaemia. RO water treatment was followed by a fall in plasma aluminium and a return of the Hb and MCV to their previous levels following a period where the Hb was raised artificially by transfusion. This patient has not required transfusion for nine months. He developed symptomatic osteomalacia which has now improved.

**Discussion**

The anaemia of chronic renal failure is characteristically normochromic and normocytic. Haemodialysis often results in an improvement in anaemia provided adequate iron supplements are given to prevent iron deficiency due to the considerable blood loss entailed in haemodialysis. Iron absorption has been shown to be normal in dialysis patients [7] and oral iron supplements will normally maintain haemoglobin at reasonable levels, making transfusion unnecessary [8]. Serum ferritin is regarded as the best and simplest measure of iron stores available for erythropoiesis [9,10]. It was, therefore, surprising that these patients developed a severe anaemia with the features of iron deficiency at a time when serum ferritin levels were normal or raised and there was no abnormal blood loss.

There is now considerable evidence that aluminium intoxication is the cause of encephalopathy [1–3] and severe osteomalacia [4] in haemodialysis patients. Increasing anaemia has been suggested as a further effect of aluminium accumulation
but this has not been further qualified [5]. Our findings suggest that aluminium intoxication causes a microcytic hypochromic anaemia that precedes the onset of osteomalacia and encephalopathy and furthermore that this anaemia improves when the source of aluminium is removed. Although it seems likely that aluminium is responsible, the role of other trace elements cannot be excluded. The development of this form of anaemia coinciding with the accumulation of aluminium and its recovery as the plasma concentrations of aluminium fell, suggests an effect on erythropoiesis. However, the site and mechanism of action on erythropoiesis is unknown. The effect of aluminium on part of the synthetic pathway for haem has been studied in vitro [11] but what the effect would be of high concentration in vivo is unknown. Our observations might explain resistance of anaemia to iron therapy in haemodialysis patients in areas having significant concentrations of aluminium in their water supplies. Now that serum ferritin and aluminium assays are more widely available, identification of these patients should be easier and will allow the appropriate therapy to be instituted before the development of osteomalacia or encephalopathy.

The source of the aluminium which causes disease in haemodialysis patients has been the subject of considerable debate. Aluminium hydroxide given by mouth to control plasma phosphate concentration and aluminium in water used to make up dialysis fluid have both been held responsible. Although there is evidence that ingestion of large quantities of aluminium hydroxide may have been responsible in some cases [1] the major factor is now thought to be the presence of a significant concentration of aluminium in dialysis fluid [2,4,12]. All our patients continued to take oral aluminium hydroxide, yet the plasma aluminium fell with improvement of anaemia and bone disease. This adds further weight to the argument in favour of dialysis fluid being the major source of aluminium. Whether the fall in plasma levels in our patients resulted from aluminium being removed by dialysis, deposited in tissues or excreted in significant amounts in faeces and urine is unclear. Aluminium is highly protein bound and dialysis against aluminium free dialysate probably results in removal of only very small quantities [13]. The study of net aluminium balance must await a reliable means of monitoring total body aluminium over a long period.

Acknowledgments

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References

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Open Discussion

DRÜEKE (Paris) When you introduced reverse osmosis to purify your water, you not only eliminated aluminium but also other trace metals. My question is, how are you sure that the metal which was responsible for your microcytic anaemia was aluminium rather than another trace metal?

SHORT I must admit I expected this very question. I cannot say that this is aluminium. We have excluded lead. There are other things which we have to look for yet.

PARSONS (Chairman) We've looked at the collection of other trace elements in uraemic bone, and there is no evidence whatsoever that any other toxic element that you can find on neutron activation is collecting significantly in bone. If it is something that is being removed by reverse osmosis it really is a very mysterious ion.

SHORT Or something unique to our water supply.

PARSONS Or a very special Scottish whisky