EVIDENCE FOR ALUMINIUM ACCUMULATION IN RENAL FAILURE

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Summary

There is increasing evidence that aluminium accumulation in patients with impaired renal function has pathological consequences. The serum aluminium content of 45 patients with chronic renal failure was found to be significantly elevated when compared with normal subjects. A further rise in serum aluminium concentration was seen in patients with chronic renal failure when they were taking aluminium-containing phosphate binding agents. Patients with stable but moderately impaired renal function who are taking aluminium-containing phosphate binders for several years may be at risk from aluminium accumulation and the development of osteomalacia and encephalopathy as seen in patients on intermittent haemodialysis.

Introduction

Aluminium is the most abundant metal on earth and appears to have no ‘essential’ biological function in man, but is only found in extremely small quantities in human tissue [1]. This suggests that a very effective mechanism operates to prevent aluminium accumulation in man. In patients with chronic renal failure maintained on intermittent haemodialysis grossly elevated levels of aluminium have been found in blood, bone, brain, liver and muscle [2–4]. These grossly elevated tissue levels of aluminium have correlated with the appearance of two pathological syndromes, dialysis encephalopathy [5] and one type of osteomalacic dialysis osteodystrophy [6]. The major source of aluminium appears to be the water supply used to prepare dialysate [7,8]. However, the role of aluminium-containing phosphate binding agents in relation to aluminium accumulation in uraemic man is uncertain. Hyperaluminaemia from oral ingestion of aluminium-containing medications was first documented by Berlyne et al [9] using neutron activation analysis and has been confirmed by other workers using atomic absorption spectrophotometry and electrothermal atomisation [10].
Clarkson et al [11] using balance techniques showed a positive aluminium balance in patients with moderately impaired chronic renal failure taking aluminium-containing phosphate binding agents. The present study was undertaken to try and establish whether aluminium accumulation in serum and bone occurred prior to the development of end stage renal failure using the recent improvements in methodology in the measurement of aluminium and whether the aluminium-containing phosphate binding agents made a significant contribution to aluminium accumulation.

Patients Studied

Forty-five patients with chronic renal failure were studied prior to requiring dialysis, 19 females and 26 males, with a mean serum creatinine of 736μmol/L, range 164–1490μmol/L, and mean age 45 years, age range 18–64 years. This group was not taking aluminium-containing phosphate binding agents. Twenty-five patients with end stage renal failure, 8 female and 17 male, mean serum creatinine 904μmol/L, range 378–1204μmol/L, and mean age 43 years, age range 18–61 years, were studied while taking aluminium-containing phosphate binding agents for a varying period of time (3 weeks to 12 years). Aluminium-containing phosphate binding agents were aluminium hydroxide gel Aludrox, Wyeth, Alucaps, Riker and Alutabs, Riker. Fifteen patients with chronic renal failure were studied before and after starting aluminium-containing phosphate binding agents (Alucaps 3–6 capsules per day containing 475mg of dried aluminium hydroxide gel in each capsule). Thirty-one normal subjects, mean age 30 years, age range 18–56 years, were used to establish the normal range for serum aluminium. Bone histopathology and aluminium content were measured in 9 patients with chronic renal failure who came to autopsy without being haemodialysed (5 female, 4 male, mean age 55 years, age range 28–68 years). Bone aluminium content was measured by neutron activation analysis (Dr C Goode and Dr J Herrington, AWRE, Aldermaston). Bone histomorphometry was undertaken using the previously described methods of Ellis and Peart [12].

Measurement of Serum Aluminium

Serum aluminium was measured using a Perkin Elmer 603 atomic absorption spectrophotometer and an HGA 76B electrothermal atomiser. Blood was obtained using a variety of plastic cannuli that had previously been screened and shown to be aluminium-free. Blood was initially transferred to acid-leached plastic containers, also previously shown to be aluminium free. Using a 2 : 1 dilution of serum with a 10 : 1 solution of triton X100, a 20μl sample was analysed in triplicate. The HGA 76B electrothermal furnace was programmed as follows:

- Drying Phase — 100°C for 20 seconds
- Ashing Phase — A ramped increase in temperature of 44°C per second to 1,500°C and held for 20 seconds
- Atomisation — 2,700°C for 6 seconds (miniflow)
Using this method and using standard additions it is possible to achieve a sensitivity of 38pg representing 44 milliabsorbance units (1% absorption), and a detection limit of 1.8µg/L for serum.

**Results**

*Serum Aluminium Content*

Table I and Figure 1 show the serum aluminium concentration in the three groups and show a significant increase in the aluminium content between the normal subjects and patients with chronic renal failure not exposed to aluminium-containing phosphate binding agents (P 0.01). There is a further striking rise in the serum content of aluminium in patients with chronic renal failure taking

<table>
<thead>
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<th>µg/L mean SD</th>
<th>Range</th>
<th>P</th>
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<tbody>
<tr>
<td>Normal</td>
<td>(31) 6.2 ± 3.1</td>
<td>1–15</td>
<td>0.01</td>
</tr>
<tr>
<td>CRF</td>
<td>(45) 13.4 ± 6.6</td>
<td>5–30</td>
<td>0.01</td>
</tr>
<tr>
<td>CRF (PO₄ binder)</td>
<td>(25) 56.0 ± 7.9</td>
<td>4–320</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>(23) 34.1 ± 23.6</td>
<td>4–75</td>
<td></td>
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(t-test with unequal variance)

Figure 1. Serum aluminium in normal subjects and patients with CRF with and without aluminium-containing phosphate binders

590
aluminium-containing phosphate binding agents (P 0.01). When the two patients with the highest serum aluminium content are excluded the statistical significance improves: P 0.001 using a t-test with unequal variance. Two patients had been exposed to aluminium-containing phosphate binding agents for 3–10 years and had a serum aluminium content of 296 and 320μg/L. Figure 2 shows the

![Graph showing the relationship between serum aluminium and Al compounds before and after treatment with aluminium compounds.](image)

Figure 2. Serum aluminium concentrations of chronic renal failure patients (15) before and after treatment with aluminium compounds.

significant rise in serum aluminium content in 15 patients with chronic renal failure before and after taking aluminium compounds for 1–3 months in a paired study. Mean serum content of aluminium 13μg/L ± 6μg/L increasing to a mean serum aluminium content of 29μg/L ± 23μg/L.

**Bone Histology**

Nine patients with chronic renal failure were studied (Table II). Seven patients had evidence of secondary hyperparathyroidism with osteitis fibrosa – score 1–2.5. Two patients had osteomalacia, defined as an increase in the number of osteoid lamellae greater than 4 (9 and 13 in these two patients) and a reduction in the calcification front. The other 7 patients had no evidence of reduction in calcification front, and osteoid lamellae were normal in number. The bone aluminium content of these patients with chronic renal failure was higher than a control group of 8 subjects, age range 19–75, where the mean aluminium content was 5.7 ± 1 (range 2–10ppm). One patient with osteomalacia had an aluminium content of bone of 93ppm. The histological characteristics of the bone of this patient were widened osteoid seams, a gross increase in the number of osteoid lamellae (13) and few inactive osteoblasts on the surface of the osteoid and some evidence of secondary hyperparathyroidism (osteitis fibrosa score of 2). (For methodology see Ellis and Peart [12]).
TABLE II. Bone Histology and Aluminium Content

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>OF Score</th>
<th>OM Score</th>
<th>Aluminium PPM/ASH</th>
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<tbody>
<tr>
<td>1</td>
<td>28 F</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>48 M</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>49 F</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>49 F</td>
<td>2</td>
<td>+(9)</td>
</tr>
<tr>
<td>5</td>
<td>53 F</td>
<td>1.5</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>64 F</td>
<td>2</td>
<td>++(13)</td>
</tr>
<tr>
<td>7</td>
<td>68 M</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>61 M</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>9</td>
<td>65 M</td>
<td>2.5</td>
<td>2</td>
</tr>
</tbody>
</table>

Mean 22.6 ± 9.2 (2–93)

Control group 8 age 19–75 aluminium content 5.7 ± 1 (2–10)

Aluminium content by neutron activation analysis
+

Osteomalacia

( ) = Number of osteoid lamellae

Discussion

There is a small significant rise in serum aluminium concentration in patients with chronic renal failure not exposed to aluminium-containing phosphate binding agents with a further strikingly significant elevation of serum aluminium in those patients with chronic renal failure who subsequently take aluminium-containing phosphate binding agents. This finding is consistent with the reports from other studies [10,13]. The rise in serum aluminium concentration is variable with some patients remaining within the normal range and others showing a marked elevation of more than 15 times the upper limit of normal. The reason for this variability is not yet understood but protein binding, residual renal function, and non-compliance with recommended dosage regimes and the presence of food in the intestine with the phosphate binding agent may all be relevant. We were unable to find a significant correlation between serum aluminium and serum creatinine.

As the kidney is likely to be the major excretory pathway for aluminium in man (as in the dog [14]) the long-term exposure to aluminium-containing compounds is likely to be of significance as patients with renal impairment may now survive many years and haemodialysis itself probably does not reduce the total body burden of aluminium to any significant degree [15]. Patients at risk appear to be those with relatively stable or slowly deteriorating renal function who are taking phosphate binding agents for a considerable period of time. Though the serum content of aluminium is unlikely to be a true reflection of total body burden it may give a guide to aluminium accumulation. Although aluminium accu-
mulation has proven pathological consequences in patients on haemodialysis [3,5] we are suspicious that aluminium may also be toxic to patients prior to end stage renal failure. The patient with severe osteomalacia (osteoid lamellae 13) and grossly elevated aluminium content of bone (93ppm), has a similar osteomalacic syndrome to that seen in our patients on intermittent haemodialysis who have been exposed to high levels of aluminium in the dialysate [6]. This 63-year old lady ingested 30–100ml of aluminium hydroxide gel (Aludrox) daily for more than 3 years. Her serum phosphate concentration was never recorded below the upper range of normal and was frequently elevated (1–2.6 mmol/L) despite the phosphate binding agent. She also developed severe myopathy and progressing intellectual impairment three months prior to death. (Unfortunately brain tissue was not available for analysis.) It would therefore seem prudent to use aluminium-containing phosphate binding agents with care and monitor serum aluminium content especially in those most at risk. Further studies into aluminium accumulation in patients with chronic renal failure prior to dialysis are urgently needed.

Acknowledgments

We would like to acknowledge the help of Dr C Goode and Dr J Herrington at the Chemistry Division, AWRE, Aldermaston, for the measurement of the bone aluminium content by neutron activation analysis. The atomic absorption spectrophotometer and electrothermal atomiser were purchased through a grant from the Medical Research Council. ISP was supported by the Scientific and Research Committee from Newcastle Area Health Authority (Teaching) and the Northern Counties Kidney Research Fund.

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Open Discussion

LEGRAIN (France) I want to confirm entirely your data and say that in our department we have been controlling serum aluminium levels for several years. In dialysed patients using reverse osmosis water supply who have been taking Aludrox gel for more than four years the chance of finding a level of serum aluminium higher than 300μmol/L is very high. The aluminium levels are slowly increasing so that in those patients who have been dialysed for more than five or ten years the chance of finding a high level is immense. We therefore believe that we must try now to reduce the amount of aluminium containing gels that we give to our patients. We have to control phosphate levels but it is very important not to overdose these patients with Aludrox.

WARD We entirely agree.

KAYE (Montreal) I would like to ask you what is the contribution of ingested water, because in those patients with long-standing renal failure they may be drinking large volumes of contaminated water in Newcastle.

WARD The aluminium level, even in our water, is very small compared with the load of aluminium you give as your phosphate-binding agents. If you are drinking maybe 2 litres of Newcastle tap water, your consumption of aluminium is in fact a few milligrams, whereas if you add aluminium hydroxide it may go up as high as 2gm of elemental aluminium. So there is a huge difference. We use aluminium cooking utensils, but I think that the food aluminium from pans and the water is a very small component and I think that we can demonstrate that by the slight rise we see in patients with chronic renal failure who haven’t taken the oral aluminium or any phosphate-binding agents, although it still rises.

PARSONS (London) You showed that some patients when being put on aluminium-containing binders didn’t have a rise in their serum aluminium. Animal work suggests that parathyroid hormone may well be one factor that encourages aluminium to cross the gut. I wonder whether the split between the patients that you saw that did not show a rise and the patients that did show a rise in aluminium were those who were on their way to develop hyperparathyroidism?

WARD That is a very interesting comment. We are in fact trying to look at this. We have no evidence to suggest in fact that it is the hyperparathyroidism, because we have been very conscious about giving aluminium hydroxide to our patients. In fact only the ones that have got proven levels go on it and as you can see the spectrum goes from normal to very high levels. What I don’t understand is the gross change but it may be that they are using a different preparation. There are several preparations on the market, Alucap, Alutabs, Aludrox, and Dr Alfrey and his workers have shown that the absorption from these different preparations is different. We don’t know whether the patient actually takes it when we prescribe it, which may be a significant factor. We also don’t know what effects their residual
renal function and the protein binding has. I think there is a lot more work that needs to be done in this area.

KLEINKNECHT (Paris) We also observed that in some patients long-term intake of oral aluminium containing gels could be a contributory factor in dialysis dementia. We observed, in particular, one patient who was dialysed for more than three years but who had taken aluminium gels previously for years. This patient developed neurological signs of dialysis dementia and these signs disappeared when oral aluminium gels were withdrawn, and reappeared when these gels were reintroduced. So it seems that at least in some patients the intake of aluminium gels may be an important factor leading to dialysis dementia because of increased intestinal absorption of aluminium.

DRUEKE (Paris) One further comment in favour of the Newcastle hypothesis that aluminium intoxication might be correlated with dialysis osteomalacia. In Paris we have done quantitative bone histology in some ten patients and we have done aluminium determinations on their bones, and we have found a highly significant correlation between bone aluminium content on the one hand and bone osteoid volume on the other hand. This would be a very strong argument in favour of your hypothesis.

TSUKAMATOTO (Japan) I failed to show any significant difference of plasma Al concentration between the uraemic patients who ingested Al(OH)$_3$ and those who did not. It is questionable whether Al could be absorbed from the intestine, because Al may bind to phosphate in most parts. Did you measure urinary concentration of Al during ingestion of Al(OH)$_3$?

WARD No, we haven’t done urine studies simply because we regard the use of atomic absorption spectrophotometry to measure aluminium in urine very difficult, because of the different biological composition of urine. Its variability alters the matrix and therefore alters your baseline and alters your blank level. So you have to find some stable matrix in which to be able to measure urinary aluminium and we have not yet tackled urine.

LEGRAIN (Paris) In answer to Dr Parsons’ comment, we have observed a rapid drop of serum Al values after parathyroidectomy. We agree that the serum values of patients taking the same amount of gel are different. This variation is very similar to what is observed with bismuth intoxication.

WINNEY (Edinburgh) I wonder if I could ask you if you think there may be a difference in absorption of aluminium between Alucaps and Aludrox? Can I mention two reasons for making this point. Firstly, in dialysis patients in Edinburgh in the home who are not using high aluminium water and only taking Alucaps and have been on dialysis for up to ten years, none of them have an aluminium exceeding 4 $\mu$mol/L. One of the patients was six months ago changed from Alucaps to Aludrox because of the poorly controlled phosphate. Until that time the plasma aluminium had been 4$\mu$mol/L and it has subsequently risen dramatically up to 16$\mu$mol/L without any other changes in the dialysis treatment. I wonder if more aluminium was available from Aludrox gel than Alucaps.

WARD We have not studied it, but I think I rather indicated during the talk
that the actual pharmaceutical preparation will be extremely important. I don’t know what the Alucaps capsule coating is, but it is very well reported that sometimes capsules do not actually dissolve and come out in the faeces. Therefore breakdown of the capsule is extremely variable. We know very little about the actual timing of giving these drugs; whether you should give it with food, or between meals or whether the phosphate in the diet is important. If you have got a lot of phosphate, well maybe a lot of aluminium is bound and so is not available for absorption, but if you have got people who are eating poorly and taking a low phosphate diet, they may in fact have a high amount of aluminium in their gut for absorption and I think there are a lot of unanswered questions.

KOKOT (Chairman)  Have you some data about the degree of contamination of the aluminium compound you used in your patients with other trace elements?

WARD  No, we have no information on that.