RISK OF ORALLY ADMINISTERED ALUMINIUM HYDROXIDE AND RESULTS OF WITHDRAWAL

F Bournerias, N Monnier, R J Reveillaud

Centre Hospitalier, Saint-Cloud, France

Summary

In 23 haemodialysis patients, taking regularly aluminium hydroxide (Al(OH)₃) of various dosage regimens for more than 18 months, three developed aluminium (Al) related morbidity (fracturing osteopathy 3/3, encephalopathy 2/3, 1/3 died).

In 15 patients followed for 14 months after Al(OH)₃ withdrawal the previously elevated serum Al concentrations fell and no worsening of osteodystrophy (especially hyperparathyroidism) could be demonstrated.

Our data and other reports suggest that oral administration of Al containing phosphate binders causes unacceptable morbidity for an unproven benefit, and should be avoided.

Introduction

Despite remaining controversies, there is now increasing evidence that orally administered aluminium (Al) containing phosphate binders, principally aluminium hydroxide (Al(OH)₃), are implicated in dialysis encephalopathy [1] and a particular form of renal osteodystrophy [2].

However, in 1981 90 per cent of European haemodialysis (HD) centres reported using routinely Al containing gels, and only 14 per cent monitored Al serum concentrations regularly [3].

We report here our experience in a haemodialysis centre with a low water Al concentration.

Patients and methods

Patients

Twenty-three haemodialysed patients were studied (11 male, 12 female, mean age 54 years). All were continuously dialysed in our centre and all received
various dosage regimens of Al(OH)$_3$ (3–12g/day) for more than 18 months (18–104, mean 55 months) without significant interruption. None presented chronic active hepatitis or other severe intercurrent diseases (prior to October 1981).

Dialysis schedule

All patients were haemodialysed 3 x 4 or 5 hours weekly on a standard dialysate (Ca content 1.75mmol/L).

Water treatment was by conventional softening; it remained unchanged during the study. Water and dialysate Al contents were assayed each six months from 1979 and were constantly <20µg/L (<0.75µmol/L).

Laboratory analyses

Blood samples were obtained immediately before dialysis in each patient and serum calcium (Ca), phosphate (P) and alkaline phosphatase were measured monthly by standard autoanalyser.

Serum Al concentrations were measured by flameless atomic absorption spectrometry, using a graphite furnace, six monthly from 1979 to 1981, and at three and 14 months after Al(OH)$_3$ withdrawal.

Immunoreactive parathormone (iPTH) was measured by radioimmunoassay (CEA antibody detecting C terminal fragment), three months before and 14 months after Al(OH)$_3$ withdrawal.

Radiology and EEG

All patients had an EEG study in 1981, and those with abnormalities again in 1982.

X-ray films of the bones (hands and acromio-clavicular joints) were performed routinely each six months. Films from 1981 and 1982 were closely reviewed, especially for signs of hyperparathyroidism.

Statistical methods

Statistical analysis was performed using the paired Student’s t-test.

Results

During Al(OH)$_3$ use, serum Al concentrations were elevated (Figure 1) (five patients had Al <50µg/L and high P, suggesting poor compliance).

In 1980–1981, three patients developed Al-related pathology (Table I), two improved markedly after Al(OH)$_3$ was stopped, and one died. EEG studies demonstrated abnormalities in six other patients (grade 1 in four patients, grade 2 in 2) [4].

Complete withdrawal of Al(OH)$_3$ was instituted in October 1981, and patients were given low doses (2–6g/day) of calcium carbonate (CaCO$_3$). The treatment
regimen remained otherwise unchanged.

Of the 22 surviving patients, 15 were followed-up for 14 months after Al(OH)$_3$ was stopped, and seven were lost for follow-up (two died of unrelated causes, four were transferred and one was transplanted). Laboratory results and X-ray films were compared before and after Al withdrawal in these 15 patients.

Serum Al fell dramatically (Figure 1) and remained low for all patients. No new cases of encephalopathy or fracturing osteopathy were observed. The EEG improved in two out of the four patients with repeat studies.

Serum P increased significantly (Table II) (over 2.5 mmol/L in only three patients) and serum Ca remained stable.
TABLE I. Three cases (out of the 23 patients) of Al-related morbidity in 1980–1981, with main clinical features (+: present; 0: absent), Al and P concentrations at time of maximal clinical signs and outcome after Al(OH)₃ withdrawal

<table>
<thead>
<tr>
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<th>Case number</th>
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<tr>
<td></td>
<td>1</td>
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<tr>
<td>Age/sex</td>
<td>61/F</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>+</td>
</tr>
<tr>
<td>Fracturing osteopathy</td>
<td>+</td>
</tr>
<tr>
<td>Al administration (months/g per day*)</td>
<td>32/3</td>
</tr>
<tr>
<td>Maximal serum Al (µg/L)</td>
<td>570</td>
</tr>
<tr>
<td>Serum P (mmol/L)</td>
<td>1.5</td>
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<tr>
<td>EEG (grade)†</td>
<td>3</td>
</tr>
</tbody>
</table>

**OUTCOME**

- Died‡
- Improved§
- Improved

* Duration of Al(OH)₃ administration and daily dosage in the six months preceding clinical signs.
† EEG alterations, grades: 0–3 in [4].
‡ Presence of microcytic, non-sideropenic anaemia.
§ Cerebral CAT scanning: mild atrophy

TABLE II. Comparison of laboratory investigations and X-ray films of the bones (hands and acromio-clavicular joints), performed before (1981) and 14 months after (12–1982) complete Al(OH)₃ withdrawal, in the same 15 patients

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<tbody>
<tr>
<td>Serum P (mmol/L)</td>
<td>1.8 ± 0.3</td>
<td>2.1 ± 0.4</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Serum Ca (mmol/L)</td>
<td>2.3 ± 0.2</td>
<td>2.4 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Serum alkaline phosphatase (IU/L*)</td>
<td>200 ± 110</td>
<td>203 ± 120</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma iPTH (ng/ml†)</td>
<td>4.5 ± 1.9</td>
<td>3.9 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Bone X-ray films‡</td>
<td>No detectable changes</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

* Normal values (not dialysed) <210 IU/L
† Normal values (not dialysed) <1.6 ng/ml
‡ Double lecture (one ‘blind’)

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No detectable worsening of hyperparathyroidism was seen during the 14 months following Al(OH)$_3$ withdrawal: serum alkaline phosphatase remained unchanged, plasma iPTH showed a slight but not significant decline, and comparison of X-ray films (1981 versus 1982) showed no detectable changes.

In addition, no patient complained of new bone or muscular pain or of pruritus (vitamin D derivatives were stopped in two cases because of mild hypercalcaemia, and CaCO$_3$ in two others for digestive complaints).

Discussion

Our study, in agreement with that of others [1, 2, 5, 6] demonstrates that the oral administration of Al(OH)$_3$ in haemodialysis patients may lead to Al accumulation, encephalopathy, fracturing osteopathy and occasionally death. In our patients Al-related symptoms and elevated serum Al were partially or fully reversed after Al(OH)$_3$ withdrawal.

Although the toxic role of water Al is clearly predominant in some areas [4], it may have been overemphasised. With the improvement of dialysis water treatment (reverse osmosis and deionisation) in affected centres, this route of intoxication is under control.

The true incidence of morbidity and mortality related to orally administered Al remains unknown. The EDTA 1981 report showed striking discrepancies between countries in reporting encephalopathy and in the use of Al containing gels, and a low rate of regular serum monitoring of aluminium [3]. Such data must be interpreted with caution, but one may infer a great disparity in appreciating the risks of oral Al exposure, probably with an overall underestimation.

Moreover, our data and others [7] suggest that the use of Al(OH)$_3$ for hyperphosphataemia is not as an effective means as generally supposed in the control of secondary hyperparathyroidism in HD patients (who can be treated in severe cases by subtotal parathyroidectomy, a safe and effective procedure).

Many unanswered questions are still pending, which our study did not address, particularly the disparity of serum Al between individual patients (Al hyper-absorption or poor Al compliers) and problems in tissue redistribution [5].

Another important point is the proposal that low Al(OH)$_3$ dosage regimens (i.e. 2g/day) may not be harmful if serum Al is strictly monitored [2–6]; but the literature shows a tendency to reduce the ‘safe serum Al concentration’ with time and so this assertion remains unproven.

The search for an ideal phosphate binder continues. CaCO$_3$ is not perfect [8]. Magnesium hydroxide has been proposed [1, 9], but well controlled studies are highly desirable before its routine use in dialysis patients.

All the evidence suggests that oral Al(OH)$_3$ administration to HD patients causes an unacceptable morbidity which outweighs a still unproven benefit, and that the warning of Berlyne and others was correct [1, 2, 6, 10]. Al containing phosphate binders should be avoided in dialysis patients.

Acknowledgments

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