ASSESSING THE BENEFIT OF CHANGING ALUMINIUM HYDROXIDE SCHEDULE ON ANAEMIA AND SERUM PHOSPHORUS CONTROL

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Summary

Convincing evidence exists concerning aluminium hydroxide (Al (OH)$_3$) absorption and risk of toxicity. Over recent years our aim has been to reduce exposure to this risk. In this study we evaluated the effect of changing our Al (OH)$_3$ prescription policy, reducing its intake by stopping the breakfast dose, separating the iron intake from the binder’s influence, and tailoring the Al (OH)$_3$ dose according to the protein intake patterns. The change was done gradually, initially in a pilot group and then in the whole unit.

The results from the pilot group, who completed two years follow-up and from the whole unit, when more patients adhered to the new scheme, were similar. After the Al (OH)$_3$ reduction serum phosphorus did not change, haemoglobin increased and the blood transfusion requirements decreased. These results support our preliminary findings that Al (OH)$_3$ might interfere with erythropoiesis and stress the necessity of reassessing the prescription of binders thoroughly, aiming to give adequate individual doses according to the different protein intake patterns.

Introduction

There is increasing evidence that aluminium (Al) can induce anaemia. Most data comes from studies with high-aluminium exposure either in haemodialysis patients dialysed with high-aluminium dialysate or in experimental works with aluminium-intoxicated animals [1–5]. Nevertheless, little has been published about the likely toxic effect of aluminium hydroxide (Al (OH)$_3$) on erythropoiesis.

In previous studies we drew attention to the need for reassessing phosphate binders in chronic renal failure as in many countries the daily phosphorus (P) intake is divided between two rather than three meals. We also demonstrated benefits achieved by separating the oral iron intake from the influence of the binder [6].
In this study we progressively evaluated over a six year period the binder efficacy of changing the Al (OH)₃ prescription policy, together with influence on the control of anaemia in an increasing number of patients on haemodialysis.

Patients and methods

We have studied a total number of 57 patients on haemodialysis. From years one to six (Table I) dialysis was thrice weekly (13.5hr/week) employing de-ionised water with an aluminium content ranging between 0.1 to 0.6µmol/L and using dialysers 1.0 to 1.3m². The daily protein intake was between 1.2 to 1.5g/kg/day, and all patients received either oral or intravenous water soluble vitamin supplements and oral ferrous sulphate in a single fasting dose of 150–300mg/day. Intravenous iron was used as has been previously described [6] for short periods without stopping the oral iron in those patients who did not respond to the oral supplements.

Throughout the study we had a very restrictive policy about transfusions using blood or packed red cells only when symptoms of anaemia became unacceptable.

TABLE I. Patients included in the study. The cumulative number (No.) and percentage refer to patients on haemodialysis (HD) who have completed at least 12 months with the new Al (OH)₃ policy

<table>
<thead>
<tr>
<th>Years</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients in the HD unit</td>
<td>27</td>
<td>30</td>
<td>39</td>
<td>42</td>
<td>45</td>
<td>57</td>
</tr>
<tr>
<td>No. and percentage of patients included in the new Al (OH)₃ policy</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>18</td>
<td>27</td>
<td>57</td>
</tr>
</tbody>
</table>

(23%) (43%) (60%) (100%)

† Beginning of the pilot group

The change in the Al (OH)₃ prescription policy is shown in Figure 1. We reduced the Al (OH)₃ intake by stopping the breakfast dose giving it twice or occasionally once, with main meals and tailoring the dose according to each patient’s protein intake pattern.

The above described change in the Al (OH)₃ intake policy was deliberately introduced gradually throughout years two to six (Table I) with the aim of diminishing the almost inevitable error implicit in comparing pre and post values over periods longer than one year and simply attributing the better performance achieved to technical improvements.

The preliminary results from the first 27 patients included in this study (pilot group) have been previously reported [6] after being treated for one year with the new policy. Twenty-two of them completed two years follow-up and they will be briefly analysed here again, as a separate group. As the change
was gradually introduced approximately one-third of the patients had completed
the two years follow-up in year four, the second third in year five and the rest in
year six (Table I).

![Diagram showing change in Al(OH)₃ policy]

**Figure 1.** Change in the Al(OH)₃ prescription policy

**Statistical analysis**

All values are expressed as a mean ± SD and they were compared using paired
and unpaired ‘t’ tests.

**Results**

The main results from the whole unit are displayed in Table II showing the
benefits achieved according to the progressive adherence of patients to the new
policy.

Despite the Al (OH)₃ intake reduction the serum P did not change, the
haemoglobin (Hb) increased, and the number of units of blood transfused
decreased significantly (p<0.05). In year six we started measuring serum aluminium
levels finding at the end of this year a serum mean aluminium level of
2.75 ± 1.8µmol/L.

The pilot group showed similar results. The significant Al (OH)₃ reduction
did not modify the serum P control (1.6 ± 0.3 to 1.6 ± 0.4mmol/L) nevertheless,
the Hb increased from 8.0 ± 2 to 9.4 ± 3 remaining stable throughout the second
year and the number of blood transfusion requirements decreased from 3.19 to
1.22 units per patient year. At the end of this period only three out of 11
checked patients had serum aluminium values higher than 2.5µmol/L and the
mean corpuscular volume was 84 ± 4µ³.
TABLE II. Main results from the whole haemodialysis unit throughout years 1–6

<table>
<thead>
<tr>
<th>Years</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al (OH)$_3$ Intake (g/day)</td>
<td>2.1 ± 1.6</td>
<td>2.6 ± 1.8</td>
<td>1.6 ± 1.1</td>
<td>1.0 ± 0.7</td>
<td>1.1 ± 0.9</td>
<td>1.2 ± 1.1</td>
</tr>
<tr>
<td>Serum P (mmol/L)</td>
<td>1.7 ± 0.4</td>
<td>1.6 ± 0.4</td>
<td>1.6 ± 0.4</td>
<td>1.7 ± 0.5</td>
<td>1.7 ± 0.4</td>
<td>1.7 ± 0.5</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>7.4 ± 2</td>
<td>7.4 ± 2</td>
<td>7.8 ± 2</td>
<td>8.6 ± 3</td>
<td>*</td>
<td>8.4 ± 3</td>
</tr>
<tr>
<td>Blood Transfusion (units/patient year)</td>
<td>–</td>
<td>2.6</td>
<td>2.8</td>
<td>1.8</td>
<td>1.7</td>
<td>1.2</td>
</tr>
</tbody>
</table>

* p<0.02, ** p<0.05, compared with values from years 1 and 2

Discussion

For some years the main source of aluminium in haemodialysis has been the dialysate prepared using untreated tap water. However, currently most haemodialysis units use adequate water treatment systems and thus Al (OH)$_3$ ingestion has become proportionately more important as an aluminium source and it merits particular attention.

Nowadays, there is no doubt about the risk of aluminium absorption from aluminium containing phosphate binders, and recently some authors have demonstrated elevated serum aluminium levels and bone toxicity in renal patients receiving Al (OH)$_3$ who were not undergoing dialysis [7,8]. As aluminium accumulates in bone inducing a form of osteomalacia it might also act in the bone marrow interfering with red cell production [4]. Although this mechanism can be valid for partially explaining the aluminium-induced microcytic anaemia, we have also proposed that Al (OH)$_3$ could interact with iron absorption either through gastroduodenal pH elevations or by its action as an iron binder in the gastrointestinal tract [6] providing another factor impairing erythropoiesis.

Even though mean serum ferritin levels have been reported as normal in dialysis patients [3,4] in our experience there are a number of haemodialysis patients with low or 'low-normal' serum ferritin levels which we believe should be interpreted in a different way than those similar results in non-renal patients. Recently with the advent and use of better developed dialysers (low-priming volume, low residual-blood volume, better washback, etc) blood loss has decreased. Nevertheless, most haemodialysis patients including ours received similar oral ferrous sulphate supplements. Therefore, if the iron were adequately
absorbed from the gastrointestinal tract and providing there are no other blood losses, one would expect most of them to have a tendency for impaired erythropoiesis and consequently a low-iron utilisation.

In fact, in one recent study seeking a likely effect of serum ferritin on gastrointestinal aluminium absorption, we found 43 per cent of patients to have low or ‘low-normal’ serum ferritin levels [9].

The significant haemoglobin improvement and the striking reduction in blood transfusion requirements after reducing the Al (OH)₃ intake and separating the iron intake from the binder’s influence in both the pilot group and the whole unit, suggest that Al (OH)₃ might interfere with erythropoiesis. Unfortunately, this study does not contain enough data to support the previously mentioned hypothesis. Nevertheless, bearing in mind the low mean serum aluminium levels, the results obtained allow us to think that in some cases not only direct aluminium toxicity is of importance. Al (OH)₃ could also be implicated through its interaction with iron in the gastrointestinal tract and impairing its absorption.

On the other hand, Al (OH)₃ has proved its efficacy in lowering serum P and although new phosphate aluminium-free binders are being developed [10] Al (OH)₃ is, so far, the most used phosphate binder and therefore all the recent warnings about its hazards should be considered thoroughly, and the dose tailored individually according to different protein intake patterns.

References

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