GASTROINTESTINAL ALUMINIUM ABSORPTION: IS IT MODULATED BY THE IRON-ABSORPTIVE MECHANISM?
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Summary

Gastrointestinal aluminium (Al) absorption has been proved but its mechanism is still unknown. This study investigates the pattern of Al absorption in patients with different degrees of iron stores.

We studied 29 haemodialysis patients forming three groups according to their serum ferritin values. Over seven days all patients received the same dose of aluminium hydroxide after which patients with ‘low-normal’ and normal serum ferritin increased their serum Al proportionally with the increased aluminium hydroxide intake. By contrast patients with high serum ferritin did not show any change in their serum Al values.

Our results therefore suggest that a ‘common pathway’ of metal absorption could be implicated in Al absorption. Serum ferritin might be a valuable predictor of different behaviour.

Introduction

The risk of aluminium (Al) absorption from Al-containing phosphate binders is almost universally accepted [1–3]. Moreover, some authors have recently reported that patients not undergoing haemodialysis who were only exposed to oral Al can develop bone toxicity [2,3] as has been previously demonstrated in patients intoxicated with Al through high-Al dialysate exposure.

An Al-free phosphate binder has been synthesised [4] but requires further evaluation, and meanwhile Al-containing phosphate binders remain the standard drug for reducing serum phosphorous in chronic renal failure. In recent years great interest has centred on studying the likely factors modulating gastrointestinal Al absorption which may help us to recognise the Al ‘hyperabsorbers’.

This study investigates whether haemodialysis patients with low-normal, normal and high iron stores have similar or different patterns of Al absorption.
Patients and methods

We studied 29 patients dialysed thrice weekly with the same schedule, aged 29 to 65 years (mean 40.6), time on haemodialysis 37.6 ± 25 months, using hollow fibre and plate dialysers 1.0–1.3 m² and employing deionised water with an Al content of less than 0.3 μmol/L throughout the study. All patients were receiving oral water-soluble vitamin supplements and a single fasting dose of 100–300 mg of ferrous sulphate as has been previously described [5].

We measured serum Al by inductively coupled emission spectrometry, serum ferritin by enzyme-immunoassay (ELISA) and parathyroid hormone (PTH) by a human C terminal radioimmunoassay (INC) which is reactive to the 65–84 sequence of human PTH (normal values less than 1.5 ng/ml).

The patients were separated into three groups according to their serum ferritin concentrations:

- **Group I:** Serum ferritin below 100 ng/L (low-normal ferritin group)
- **Group II:** Serum ferritin 100–250 ng/L (normal ferritin group)
- **Group III:** Serum ferritin above 250 ng/L (high ferritin group)

During the first seven days (Period I) all patients received ferrous sulphate and aluminium hydroxide (Al(OH)₃) in the dose they were currently having to maintain the serum phosphorus (P) between 1.5–1.8 mmol/L. At the end of Period I ferrous sulphate was stopped and during a further seven days (Period II) all received the same dose of Al(OH)₃ (2.8 g/day).

Samples for serum Al were taken at the end of Periods I and II.

Statistical analysis was performed by student's 't' test and all values are expressed as a mean ± SD.

Results

As shown in Table I Group III had a mean serum ferritin almost 10 times higher than Group I and significantly lower (p<0.05) haemoglobin concentration.

| TABLE I. Details of patients divided into three groups based on the same serum ferritin |
|---------------------------------|-----------|-------------|
|                                  | Group I   | Group II    | Group III   |
| Serum ferritin (ng/L)           | 100       | 100–250     | 250         |
| Mean serum ferritin             | 48 ± 23   | 149 ± 40    | 468 ± 206   |
| Number of patients (mean age)   | 13        | 10          | 6           |
| (mean age)                      | (51.6±9.9)| (50.7±9.9)  | (45.3±10.1) |
| Haemoglobin (g/dl)              | 9.1±2.6   | 8.47±1.6    | 7.13±1.6 *  |

*p<0.05 between Group I and Group III
TABLE II. Period I. Baseline results before giving 2.8g/day of Al(OH)₃ during Period II to all groups

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin (ng/L)</td>
<td>&lt;100</td>
<td>100–250</td>
<td>&gt;250</td>
</tr>
<tr>
<td>Al(OH)₃ dose (g/day)</td>
<td>2.04±1.5</td>
<td>1.44±1.9</td>
<td>0.77±1.08*</td>
</tr>
<tr>
<td>Serum P (mmol/L)</td>
<td>1.68±0.33</td>
<td>1.69±0.32</td>
<td>1.31±0.31**</td>
</tr>
<tr>
<td>Serum Al (μmol/L)</td>
<td>2.94±2.1</td>
<td>3.09±1.9</td>
<td>1.62±0.6*</td>
</tr>
<tr>
<td>Serum PTH (ng/ml)</td>
<td>5.01±3.4</td>
<td>3.57±1.9</td>
<td>3.71±1.8</td>
</tr>
<tr>
<td>Patients on 1,25(OH)₂D₃</td>
<td>8 of 13 (61%)</td>
<td>5 of 10 (50%)</td>
<td>1 of 6 (83%)</td>
</tr>
</tbody>
</table>

**p<0.01; *p<0.05 between Group I and Group III

In Period I (Table II) the significant differences (p<0.05) in serum Al results between Groups I and III can not be explained either on the basis of plasma PTH or 1,25(OH)₂D₃ intake, but by significant differences (p<0.05) in Al(OH)₃ ingestion. Despite a significantly lower use of binder, Group III achieved a significantly better serum P control (p<0.01).

Figure 1 shows that in all groups the change of Al(OH)₃ dose from Period I to Period II represented a significant increase, being the highest (p<0.001) in the high ferritin group. Nevertheless, this group was the only one who did not show any great increase in serum Al. When we compared the ratio of Serum Al/Al(OH)₃ dose, we found no significant changes in Groups I and II, so, the serum Al increase was proportional to the Al(OH)₃ change. By contrast, Group III had a highly significant change from Period I to Period II (p<0.001).

Discussion

It took many years to fully convince nephrologists about the risks of toxicity from well known Al-phosphate binders which have been used as antacids for almost half a century.

Berlyne and colleagues drew attention to Al-resin toxicity in chronic renal failure in 1970 [6] yet we are still using similar phosphate binders whose mechanisms of absorption are not certain. Al balance studies are very difficult to perform and have produced controversial and sometimes irreproducible results. Furthermore, the fact we cannot use a non-toxic labelled Al makes the absorption studies more imprecise. These problems are magnified when evaluating likely factors influencing Al absorption.

In clinical studies the best guide we have is the serum Al changes. The results of animal experiments cannot always be extrapolated to the human situation.
Figure 1. Al(OH)₃ dose, Serum Al and Serum Al/Al(OH)₃ ratio. Changes from Period I (P I) to Period II (P II)
Despite the above mentioned limitations, it is accepted that the Al intake, the kind of salt administered and its temporal relation with meals could influence absorption [1,7]. Parathyroid hormone, Vitamin D and the ‘uraemic state’ have also been blamed for enhancing Al absorption [7,8].

In previous studies we implicated Al in iron metabolism suggesting a likely interaction between them [5]. In addition some reports [9,10] have provided evidence about likely common pathways of gastrointestinal absorption between iron, lead, cadmium and cobalt, alerting us to the risk of greater and indiscriminate metal absorption in iron deficiency.

Although mean serum ferritin values have been reported as normal in dialysis patients, this study shows there is a significant proportion of patients with ‘low-normal’ serum ferritin which, judging from the haemoglobin and Al(OH)₃ results from Period I (Tables I and II) could be partially due to better iron utilisation and also to Al(OH)₃ interaction with iron into the gastrointestinal tract, as patients with lower serum ferritin concentration received significantly higher amounts of Al(OH)₃. By contrast the higher serum ferritin group was receiving a significantly lower Al(OH)₃ intake, controlling serum P even better than the others and achieving the benefit of having a low serum Al concentration. These patients were the only ones who did not have a proportional serum Al increase at the end of Period II in spite of receiving a proportionally greater Al(OH)₃ supplement (Figure 1).

Therefore, it seems that patients with high iron stores might have less chance of absorbing Al from Al(OH)₃. If so, this could explain the results in Table II regarding Al(OH)₃ requirements and serum P concentration, as they would need less Al(OH)₃ to keep serum P under control as most of the Al(OH)₃ would act as a binder in the gastrointestinal tract instead of being easily absorbed.

Therefore, from our preliminary results, we believe a ‘common pathway’ of metal absorption might be implicated in Al absorption. If so, patients with high iron stores would absorb less Al and thus the serum ferritin might be a useful predictor of Al absorption and perhaps of Al(OH)₃ requirements, helping us to recognise the ‘Al-hyperabsorber patients’. These findings would also partially explain the wide range of individual variations in gastrointestinal Al absorption.

References

2 Kaye M. Clin Nephrol 1983; 20: 208
8 Mayor GH, Sprague SM, Hournani MR, Sanchez TV. Kidney Int 1980; 17: 40
10 Barton JC, Conrad ME, Nuby S, Harrison L. J Lab Clin Med 1978; 92: 536
ROODVOETS (Haarlem, Netherlands) A high ferritin value may be due to repeated blood transfusions and therefore may not reflect the capacity of intestinal iron absorption.

CANNATA Yes, that is correct, patients from group III had received more blood transfusions. I can say from our experience that if your iron stores are repleted there is not a good stimulus to absorb iron and therefore you will not have a strong stimulus to absorb aluminium. I can't say anything about iron absorption because some of these patients have become iron overloaded from transfusions.

KERR (Chairman) Dr Cannata if your thesis is correct it is a little surprising that you have an effect upon phosphate control when you consider how little aluminium is absorbed. You are giving your patients 2.8 grams of aluminium hydroxide daily and so you are talking about gram quantities of aluminium. The changes are, in fact, measured by micro grams per litre. I don't think we know in absolute terms the amount absorbed but it is probably milligrams at the most. It is hard to see how that could alter the effectiveness of aluminium hydroxide as a phosphate binder. Would you like to comment on that?

CANNATA I too was in trouble trying to think of an explanation for that. I don't have a clear explanation and my interpretation is really a hypothesis but I don't have any hard data to support it.

KERR It is possible, surely, that your over-transfused patients differ in some way from other groups. Have you looked at their phosphate intakes to see whether there is any dietary difference?

CANNATA I have not.