Technical Report

Ultrafiltrable aluminium after very low doses of desferrioxamine

Alejandra Canteros, Carmen Díaz-Corte, Jose-Luis Fernández-Martín, Emilio Gago¹, Carmen Fernández-Merayo¹ and Jorge Cannata

Bone and Mineral Research Unit, Instituto Reina Sofía de Investigación and ¹Renal Unit, Hospital Central de Asturias, Universidad de Oviedo, Spain

Abstract

Background. The recommended dose of desferrioxamine for the treatment of aluminium intoxication is 5 mg/kg/week. However, there are no data about the efficiency of lower doses. The objective of this study was to investigate the capacity of very low doses of desferrioxamine in the generation of ultrafiltrable aluminium.

Methods. Five patients undergoing haemodialysis with a similar biochemical profile and serum aluminium levels >40 µg/l were studied. The three different doses of desferrioxamine used (0.5, 2.5 and 5.0 mg/kg) were administered randomly to each patient at 1 week intervals. Total and ultrafiltrable serum aluminium was measured before and 44 h after the administration of desferrioxamine.

Results. All doses of desferrioxamine significantly increased the total serum aluminium; no differences were found between 2.5 and 5.0 mg/kg. The total serum aluminium levels doubled with the 2.5 and 5.0 mg/kg doses, while the increase with 0.5 mg/kg was lower (32.6%, P<0.05). Ultrafiltrable aluminium increased with the three doses; from 7.1±2.8, 3.9±0.6 and 7.5±4.1 to 25.7±7.3, 44.3±10.1 and 59.1±19.8 µg/l, respectively (P<0.05). The efficiency of each dose was calculated using the ratio between the increase in ultrafiltrable aluminium and the dose of desferrioxamine administered. The efficiency ranged from 10.3±3.9 for the higher dose (5 mg/kg) to 37.2±10.3 for the lower dose (0.5 mg/kg).

Conclusions. Our results suggest that very low-dose desferrioxamine (>5 mg/kg) increases the ultrafiltrable (potentially dialysable) aluminium.

Key words: aluminium; desferrioxamine; dialysis

Introduction

Aluminium is still an important cause of morbidity in dialysis patients. Treatment of aluminium intoxication is based on the prevention of aluminium exposure [1] and increased removal of aluminium by dialysis [2,3]. Nevertheless, aluminium transfer during dialysis is limited because serum aluminium is bound to high molecular weight proteins, mainly transferrin, and, therefore, it is not dialysable.

The most effective way of removing aluminium from serum is to increase the amount of ultrafiltrable aluminium by using desferrioxamine. This drug removes aluminium from tissues [3] and increases serum aluminium levels, and may displace the aluminium bound to transferrin, forming a low molecular weight aluminium–desferrioxamine complex which is dialysable [4–6]. The percentage of ultrafiltrable aluminium after desferrioxamine administration has been reported to be >60% [7–11], with doses of desferrioxamine ranging between 10 and 100 mg/kg [7–9]. Other authors have found similar results using 5–20 mg/kg doses [12]. However, there are no data using doses lower than this.

Previous in vitro studies performed by our group showed that there is no linear relationship between the ultrafiltrable aluminium and the concentration of desferrioxamine [13]. We have also shown that low concentrations of desferrioxamine (<10 µM) significantly increase the percentage of ultrafiltrable aluminium.

The objective of this study was to investigate if very low doses of desferrioxamine increase the ultrafiltrable (potentially dialysable) aluminium.

Patients and methods

Patients

Five patients with a mean age of 61.2±12.2 years (three males, two females) with serum aluminium levels >40 µg/l were included in the study. The mean time on haemodialysis (HD) was 9.2±4.6 years (two of them had a previous renal transplantation). Three patients were on conventional HD and the remaining two patients were treated by paired filtration dialysis (PFD). Desferrioxamine was not used in the 12 months prior to the study. Haematological and biochemical values are shown in Table 1.

One week before the beginning of the study, ingestion of
Table 1. Haematological and biochemical values of the patients

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>29.0 ± 1.8</td>
<td>(25.2–32.2)</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>9.5 ± 0.9</td>
<td>(8.4–11.0)</td>
</tr>
<tr>
<td>MCV</td>
<td>88.6 ± 7.6</td>
<td>(75.7–96)</td>
</tr>
<tr>
<td>Biochemical values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.5 ± 0.6</td>
<td>(8.8–10.5)</td>
</tr>
<tr>
<td>Iron (µg/dl)</td>
<td>48.8 ± 9.5</td>
<td>(39–59)</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>134.4 ± 130</td>
<td>(62–366)</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>488.2 ± 421.6</td>
<td>(11–1201)</td>
</tr>
</tbody>
</table>

aluminium hydroxide was stopped (three patients). Iron supplementation was also withdrawn during the experiment.

Procedure

Desferrioxamine from Ciba-Geigy was administered once per week, at three different doses (0.5, 2.5 and 5.0 mg/kg) for 5 weeks, following the scheme shown in Figure 1. The order of the three different doses was assigned randomly (0.5, 2.5 or 5.0 mg/kg) with a 1 week interval between the three different doses.

Before administration, desferrioxamine was diluted using 5% glucose. The smaller dose (0.5 mg/kg), was administered in 1 min and the other two doses were infused over 10 min at the end of the dialysis session.

Samples of blood from the arterial line were drawn before and 44 h after the infusion of desferrioxamine for the measurement of total and ultrafiltrable aluminium.

In vitro ultrafiltration of all the samples was carried out according to the methodology described previously [13] using the micropartition system Amicon® (MPS-1, Danvers, MA) with a membrane nominal cut-off of 30 000 Da. An exhaustive rinsing of the membranes was performed in order to avoid contamination of the samples. The ultrafiltration (0.25 ml of serum) was performed by centrifugation at 800 g, and aluminium was measured in total serum prior to centrifugation and in the ultrafiltrate fluid obtained after passage through the membrane. Aluminium was measured by graphite furnace atomic absorption spectrometry using a HGA-600 graphite furnace coupled to a Z-3030 atomic absorption spectrometer with Zeeman background correction [13].

Statistical analysis was performed using the Wilcoxon test for two related samples and the Friedman test for several related samples.

Results

The results obtained before and after the administration of the desferrioxamine are shown in Table 2. No differences were found among the basal values (pre-DFO) for the three doses of desferrioxamine administered. Table 3 shows the increase in the total serum and ultrafiltrable aluminium after desferrioxamine administration (post-DFO–pre-DFO).

All doses of desferrioxamine (0.5, 2.5 and 5.0 mg/kg) increased the ultrafiltrable aluminium. The increase in ultrafiltrable aluminium obtained with 2.5 mg/kg was double, and that with 5.0 mg/kg was almost triple the increase obtained with 0.5 mg/kg ($P < 0.05$, Table 3). However, the doses of desferrioxamine needed to obtain such a difference were 5 and 10 times higher, respectively. Thus, if we evaluate the efficiency of each dose as the ratio of increase of ultrafiltrable aluminium to the dose administered (µg/l of ultrafiltrable aluminium per mg/kg of desferrioxamine administered), the dose of 0.5 mg/kg was more efficient than 2.5 mg/kg and the latter more efficient than 5 mg/kg (all differences $P < 0.05$) (Table 3, Figure 2).

The increase in the total serum aluminium was higher with 2.5 and 5 mg/kg desferrioxamine; no significant differences were found between these two doses (Table 3). Although 0.5 mg/kg is 10 times lower than the highest dose (5 mg/kg), the increase in total serum aluminium obtained using 0.5 mg/kg was less than five times lower than the increase obtained with 5 mg/kg.

The increase in total serum aluminium correlated with the increase in ultrafiltrable aluminium for all the doses administered (Figure 3). The slope of the regression line was close to 1 ($0.98 ± 0.11$).

Discussion

The widespread use of vitamin D resulting in difficulties in adequately controlling serum phosphorus has forced
Table 2. Total serum and ultrafiltrable aluminium before (pre-DFO) and 44 h after the administration of desferrioxamine (post-DFO) at the three different doses studied

<table>
<thead>
<tr>
<th>Dose of DFO (mg/kg)</th>
<th>Total Al (µg/l)</th>
<th>Ultrafiltrable Al (µg/l)</th>
<th>Percentage of ultrafiltrable Al (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>pre-DFO 43.2±11.8</td>
<td>7.1±2.8</td>
<td>17.5±8.1</td>
</tr>
<tr>
<td></td>
<td>post-DFO 57.3±13.7</td>
<td>25.7±7.34</td>
<td>45.6±11.7</td>
</tr>
<tr>
<td>2.5</td>
<td>pre-DFO 42.9±18.0</td>
<td>3.9±0.6</td>
<td>10.7±4.9</td>
</tr>
<tr>
<td></td>
<td>post-DFO 79.9±16.9</td>
<td>44.3±10.1</td>
<td>55.6±8.2</td>
</tr>
<tr>
<td>5.0</td>
<td>pre-DFO 50.8±19.4</td>
<td>7.5±4.1</td>
<td>15.6±6.7</td>
</tr>
<tr>
<td></td>
<td>post-DFO 102.5±38.6</td>
<td>59.1±19.8</td>
<td>58.4±5.9</td>
</tr>
</tbody>
</table>

P <0.05, pre-DFO vs post-DFO, a vs b, a vs c, d vs e, d vs f, e vs f, g vs h, g vs i, h vs i.

Table 3. Increase of total serum and ultrafiltrable aluminium 44 h after the administration of desferrioxamine (post-DFO) at the three different doses studied.

<table>
<thead>
<tr>
<th>Increase after DFO</th>
<th>Dose of desferrioxamine (mg/kg)</th>
<th>Total Al (µg/l)</th>
<th>Ultrafiltrable Al (µg/l)</th>
<th>Efficiency (UF Al/dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5</td>
<td>14.1±2.3a</td>
<td>37.0±7.5a</td>
<td>37.2±10.3a</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>18.6±5.6a</td>
<td>40.4±10.5a</td>
<td>16.1±4.2a</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>51.7±20.0a</td>
<td>51.5±19.9</td>
<td>10.3±3.9</td>
</tr>
</tbody>
</table>

P <0.05, a vs b, a vs c, d vs e, d vs f, e vs f, g vs h, g vs i, h vs i). Efficacy was calculated as the increase in ultrafiltrable aluminium/dose of desferrioxamine.

P <0.05, post-DFO vs pre-DFO.

Our results demonstrate that even very low doses of desferrioxamine (0.5 mg/kg) increase the ultrafiltrable aluminium (potentially removable by dialysis). Although the increase of total and ultrafiltrable aluminium was lower with 0.5 mg/kg compared with the other two doses (2.5 and 5.0 mg/kg), the efficacy of the lowest dose in the generation of ultrafiltrable aluminium was higher (Table 3, Figure 2). In other words, a 10-fold increase in desferrioxamine (from 0.5 to 5 mg/kg) resulted only in a 2.8-fold increase in ultrafiltrable aluminium (Table 3). The generation of ultrafiltrable aluminium in response to the administration of desferrioxamine was not linear (Table 5).

Total serum aluminium increased by 32.6% with 0.5 mg/kg of desferrioxamine, whereas with 5 mg/kg the increment was 101.7% (Table 2). Even though the increase in serum aluminium using 0.5 mg/kg might be considered low (32.6% vs 101.7%), we have to take into account that the dose of desferrioxamine used was 10 times lower. In summary, the use of very low doses of desferrioxamine would produce a lower net removal of aluminium. This approach might be used to treat patients for longer and more safely.

Our study also demonstrated that the increase in total serum aluminium correlated (r=0.925) with the increase in ultrafiltrable aluminium with a slope close to 1 (0.98). This finding indicates that the increases in serum aluminium induced by desferrioxamine are due to increases in ultrafiltrable (dialysable) aluminium (Figure 3). Therefore, the increments in total serum aluminium may be used as a predictor of the amount of aluminium to be removed with desferrioxamine. It
is widely accepted that the increase in total serum aluminium after desferrioxamine administration in the form of aluminoxamine is derived from the tissues, with little reduction in transferrin-bound aluminium [3]. However, desferrioxamine itself is able to remove aluminium from transferrin [13,16] and, at least theoretically, 44 h after the administration of desferrioxamine, the concentration of transferrin-bound plasma aluminium depends on the concentration of all the remaining ligands (i.e. free desferrioxamine, citrate, phosphate, etc.). As shown in Table 3, the increase in ultrafiltrable aluminium is very close to the increase in total aluminium for all the doses studied, demonstrating that all the doses of desferrioxamine used were able to remove aluminium from the tissues.

Previous reports have demonstrated that the response to a single dose of desferrioxamine may depend on the iron status of the patients studied [17]. Unfortunately, we do not have a complete profile of the iron stores in the five patients studied, but with the available data we should not expect a relevant influence of iron metabolism. In addition, the low dose of desferrioxamine used in this short-term study is not able to modify the iron status. Differences in response have been observed in patients with greater differences in iron stores.

The dose of 5 mg/kg has been demonstrated to be effective in aluminium chelation therapy [18] and also for the diagnosis of aluminium overload [19]. Our study suggests than even lower doses would be useful. The use of very low-dose desferrioxamine might be of value in cases of severe aluminium intoxication in order to avoid an excessive interdialysis hyperaluminaemia induced by desferrioxamine. Moreover, the use of this low dose regime would be less toxic by reducing the production of ferrioxamine, probably responsible for the side effects of desferrioxamine [20,21]. Further clinical studies are necessary to evaluate the long-term efficiency of this new strategy for the treatment and diagnosis of aluminium overload.

References


Acknowledgements. Our thanks to M. Serrano and A. González Carcedo for their technical support. This work has been partly supported by FIS 91/03329, Instituto de Cooperación Iberoamericana (ICI), Universidad de Oviedo and Fundación Renal Itígo Alvarez de Toledo. A.C. was the recipient of grants from ICI and Universidad de Oviedo.

Received for publication: 9.6.97
Accepted in revised form: 9.2.98