Efficacy of low-dose desferrioxamine for the estimation of aluminium overload in haemodialysis patients


Introduction
Aluminium toxicity in patients on regular haemodialysis has been frequently reported in the literature [1-5]. Encephalopathy and bone disease are the two most important expressions of aluminium toxicity. In patients with end stage renal disease aluminium excretion is practically nil. However, aluminium hydroxide is still one of the most prescribed phosphate binding agents in these patients [6]. This results in cumulation of aluminium in the body.

Methods for diagnosing aluminium-related bone disease presently include [7]:
- Measurement of random serum aluminium levels.
- Performance of a desferrioxamine (DFO) test.
- Performance of a DFO test combined with measurement of serum parathyroid hormone levels.
- Direct assessment of aluminium in bone by bone biopsies to determine stainable aluminium at the mineralisation front or total aluminium content.

DFO is a trihydroxamic acid and is widely used as an iron chelating agent in the treatment and diagnosis of iron overload and in iron intoxication. The compound forms 1:1 cationic complexes of high stability with iron(III) and other trivalent metal ions, and complexes of generally lower stability with divalent ions [8]. Since 1980 the chelator has been used in the diagnosis and treatment of aluminium overload in dialysis patients because DFO also binds aluminium(III) with very high affinity (theoretically 100 mg of desferrioxamine mesylate could bind 4.1 mg of aluminium [9]) and extracts aluminium from tissues into plasma. After infusion of DFO a significant rise in serum aluminium can appear. The increment is considered as a warning signal of an elevated aluminium body burden. The response is related both to the dose and to the amount of accumulated aluminium, and a one-shot infusion test is used diagnostically. The 1:1 aluminium-DFO complex disperses through the extracellular fluid volume, and is rapidly cleared by haemodialysis [8 10 11].

Assessment of aluminium in bone is considered the ‘Gold Standard’ [12], but it is an invasive method. The DFO test is noninvasive, generally well tolerated, and of value particularly in excluding the diagnosis of aluminium-related osteodystrophy [13]. However, the recommended doses of DFO (30 or 40 mg per kilogram of body-weight) may cause many side effects such as flushing, urticaria, hypotension, and shock, but also serious ocular side effects [4 9 11-13]. To investigate if a lower dose of DFO is also useful and free of side effects, we compared 500 mg DFO with 30 mg DFO per kg of body-weight in patients on regular haemodialysis. Moreover, the low-dose DFO test was assessed for its predictive value in the diagnosis of aluminium intoxication compared to the high-dose DFO test.
Patients and methods
After the approval by the hospital ethical committee, and after signing their informed consent, 22 patients (9 men and 13 women) receiving regular haemodialysis treatment for at least one year and with clinical evidence of renal bone disease, were prospectively investigated.

Study design
First we performed the high-dose DFO test with the dose recommended in the literature [16]: Thirty mg per kg of body-weight of DFO (Desferal®, Ciba-Geigy, Arnhem, The Netherlands), diluted in 250 ml 0.9% saline (Baxter, Lessines, Belgium), were administered intravenously in the first two hours of dialysis treatment. To avoid carry over effects, a low-dose DFO test was conducted six months later. During the first two hours of the dialysis treatment, a fixed dose (500 mg DFO, irrespective of body-weight, diluted in 100 ml of 0.9% saline) was administered intravenously, conforming to Yaqoob et al. [17]. Phosphate binding medication was not changed.

Serum aluminium was measured by atomic absorption spectrometry (AAS). Measurements were made by comparison with reference solutions with known concentrations of aluminium by the Method of Standard Additions. The limit of detection by this method for serum aluminium is 5 pg/l (0.19 pmol/l). The results of analysis of 20 separate samples of serum (External Quality Control Sera, University of Surrey, Guildford, UK) by our laboratory showed a good agreement with the mean target values. The mean recovery was 98.6%, with a standard deviation of 5.6%.

Statistics
Statistical analysis was performed with paired t-tests. The results are expressed as means ± SD. Linear regression analysis was used for assessing correlations.

Results
Baseline Characteristics
The baseline characteristics of the patients are summarised in Table 1.

Toxic side effects were observed in nine patients during the high-dose DFO test, mainly nausea, itching and dizziness, and in only one patient during the low-dose DFO test. This patient experienced a slight headache.

A serum aluminium increment above 40 pg/l (1.48 pmol/l) after 48 hours was chosen as the threshold level if a low dose of DFO was administered. The reason for this threshold level was that the dose of DFO administered in the latter test was approximately four times less than that in the high-dose test, and we assumed a dose-dependent response.

Dialysis Programme
Dialyses, four hours three times a week, were performed with bicarbonate and polysulfon low flux dialysers (area 1.3 m²). The dialysate was virtually free of aluminium, using water treated with reversed osmosis. The bloodflow was about 250 ml/min and the dialysate flow 500 ml/min.

Data collection
In both tests blood samples (pre-dialysis) were taken before (t1), and 48 hours after the DFO challenge (t2). With regard to the increase in the aluminium level in both tests, we found 14 patients with a high, and eight with a low increment (above or below 150 pg/l (5.56 pmol/l) or 40 pg/l (1.48 pmol/l), respectively). In six patients the outcome of the low-dose DFO test was not compatible with the outcome of the high-dose DFO test. Three patients changed from a positive to a negative test result, and three from a negative to a positive result (Figure 1). From the latter three, one patient changed from a high to a low baseline aluminium concentration, and one other from

<table>
<thead>
<tr>
<th>Table 1 Characteristics of 22 patients undergoing regular haemodialysis who received long-term phosphate binding medication with calcium carbonate and/or aluminium hydroxide. Values are means ± SD.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>9 men</td>
</tr>
<tr>
<td>13 women</td>
</tr>
</tbody>
</table>

Laboratory tests
Serum aluminium was measured by atomic absorption spectrometry (AAS). Measurements were made by comparison with reference solutions with known concentrations of aluminium by the Method of Standard Additions. The limit of detection by this method for serum aluminium is 5 pg/l (0.19 pmol/l). The results of analysis of 20 separate samples of serum (External Quality Control Sera, University of Surrey, Guildford, UK) by our laboratory showed a good agreement with the mean target values. The mean recovery was 98.6%, with a standard deviation of 5.6%.