Brief Report

Relative roles of intestinal absorption and dialysis-fluid-related exposure in the accumulation of aluminium in haemodialysis patients

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Abstract

Background. A recent retrospective study has clearly demonstrated a reduction of cases with positive bone aluminium (Al) staining in the Italian dialysis population, which in general has had a low prevalence of bone Al toxicity. In the present study we tried to better address the relative role played, in our study population, by enteral and parenteral exposure to Al in reducing bone accumulation.

Methods. We retrospectively examined the data of 105 DFO tests and bone Al determinations performed in dialysis patients from 1984 to 1995. Enteral exposure was analysed by accurate anamnestic records, while parenteral exposure was evaluated by the determination of Al content in dialysis fluids. Bone Al content was assayed chemically and histochemically, while serum Al was assayed spectrophotometrically. Data pertinent to the patients were allotted into three period groups: 1984–1987; 1988–1991; 1992–1995. As for Al concentrations in dialysis fluids, the interval 1980–1983 (immediately before the start of our study), which could clearly have influenced bone Al content, was also considered.

Results. Basal serum Al showed some fluctuations (42.7 ± 34.1; 24.8 ± 21.9 and 38.9 ± 34.9 μg/l respectively in the three groups, ANOVA P < 0.01) but only values of the period 1988–1991 were significantly lower than those of the period 1984–1987 (P < 0.05). Increments after DFO did not differ in the three periods (136.5 ± 105.7; vs 98.7 ± 91.7 and 106.1 ± 96.2 μg/l respectively, P = n.s.). Enteral exposure to drugs containing Al was comparable (4.1 ± 2.9 vs 4.0 ± 4.6 and 5.8 ± 7.9 total kg ingested respectively; P = n.s.), but bone Al was dramatically reduced (from 60.7 ± 43.0 to 29.0 ± 24.4 and 31.9 ± 29.9 mg/kg/dw respectively; P < 0.0001), along with the definite disappearance of Aluminon-positive cases and Al-related bone disease (ARBD) after 1991. Parenteral exposure through the dialysate dropped from a mean of 26 ± 14 μg/l in the 4-year period prior the start of the study (1980–1983) to 9 ± 6 μg/l in the period 1984–1987 and to 4.9 ± 2.1 μg/l and 5.0 ± 2.0 μg/l respectively thereafter (P < 0.0001).

Conclusions. Despite the persistence of oral exposure to Al, responsible for the observed stability of serum Al levels, a definite reduction of bone Al content has been recorded in our dialysis population, and ARBD has disappeared. This result has to be referred essentially to the optimal control of Al content in dialysis fluids, which is confirmed as a major factor for Al intoxication.

Key words: aluminium hydroxide; aluminium toxicity; bone aluminium; desferrioxamine test; dialysate aluminium; dialysis fluids; haemodialysis

Introduction

Although obvious reductions of both Al-related toxicity and mean serum Al in dialysis patients have certainly occurred in recent years [1,2], the possibility of a mild accumulation (and possibly toxicity) of Al still exists [3]. For instance, Malluche and Monier-Faugere [4] in a retrospective evaluation of their population, have reported an increase in the number of patients exhibiting positive Al staining (>30% of the trabecular surface), from 34% in 1982–1983 to a mean stable prevalence of 50% in the following years, up to 1991. As far as the Italian dialysis population is concerned, a low prevalence of Al-related bone disease (ARBD) has been generally reported [5,6]. Moreover, in a recent retrospective evaluation of 1429 bone biopsy samples, a reduction of cases with positive Al staining (any extent of positivity) from 35.6% in 1985 to 4.2% in 1994 has been reported [7]. The aim of the present study was to address this issue more accurately by evaluating the relative role that dialysate and intestinal-related exposure to Al have had in the reduction of bone Al accumulation.

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Subjects and methods

We retrospectively examined the data of 105 patients (56 males, 49 females; aged 51.5 ± 17.1 years) on haemodialysis treatment for 88.1 ± 47 months, who had been referred to our outpatient unit by several dialysis centres of our regional area, for the evaluation of renal osteodystrophy, in the period 1984–1995. They were studied by means of a desferrioxamine (DFO) infusion test and a transilic bone biopsy for bone Al content and histological diagnosis. The test was performed according to the following schedule: basal blood sampling before dialysis; DFO infusion at the dose of 28.5 mg/kg/bw in the last 30 min of treatment; post-DFO sampling after approximately 44 h (just before the next dialysis). At the time of the study, an accurate anamnestic assessment of oral phosphate-chelating therapy was performed. In particular, commercial types and doses of prescribed drugs were recorded, the real compliance to prescription was firmly asked for, and the mean daily and total consumption values in each patient were calculated. Moreover, those patients with possible presence of a parenteral exposure other than that related to dialysis (like parenteral nutrition, i.v. albumin etc.) were excluded from the study.

To estimate the entity of Al exposition through dialysis fluids, we have examined the data collected at the Trace Elements Unit of the Applied Toxicology Laboratory of Rome (Istituto Superiore di Sanità) from 1980 to 1995. A total of 373 samples of different dialysis fluids, were received from several industries and from the same dialysis centres referring patients to our unit. Samples were allotted as follows: 94 concentrates; 50 reinfusates; 158 deionized water, and 71 dialysates.

For the purpose of the present study, patients’ data were subdivided into three period groups: 1984–1987; 1988–1991; 1992–1995. In the case of dialysis fluids, because bone Al content may have been influenced by previous exposure, we also considered the 4-year-interval preceding our study (1980–1983).

Assay methods

Al was measured by the SPTF-AAS technique, using a Perkin Elmer 5100 Zeeman (Norwalk, Conn, USA) equipped with a HGA–600 graphite furnace and an AS–60 autosampler. A calibration curve was constructed by running different Al standards prepared in normal serum with low endogenous Al content (<3 μg/l). The standard addition method was also applied to some samples, to verify the validity of the calibration procedure. Serum samples were diluted with a mixture of magnesium nitrate 2.5 g/l plus Triton-X 100, 0.1%. Dialysis fluid samples were diluted with a mixture of HNO3 1% v/v plus Triton-X 100, 0.1% [8]. Bone biopsy specimens were washed clean of marrow, defatted, dried, and ashed in an oven before the assay [9]. Our normal values, respectively for serum and bone, are: 4.5 ± 2.0 μg/l and 2.4 ± 1.1 mg/kg/dw. During the whole period of the study the same instrumentation and assay procedures were employed and the Unit participated in some External Quality Assurance Programmes (EEC Programme and Italian QC Programme).

For histological diagnosis and histochemical studies, bone specimens were handled as previously described [10]. Sections before dialysis; DFO infusion at the dose of 28.5 mg/kg/bw 3–4 mm thick were stained using the Al histochemical staining technique (Aluminon). The histopathological diagnoses were performed according to the morphological criteria suggested by Malluche and Faugere [11]. Briefly, a general increase in bone turnover rate was designed as predominant hyperparathyroidism, while a decrease in bone turnover rate associated with an increase of both osteoid surface and thickness was regarded as osteomalacia. A local increase in bone turnover rate coexisting with focal defective mineralization were the hallmarks of mixed osteodystrophy, and a reduced bone turnover associated with thin osteoid seam, bone cell paucity, and a decrease in tetracycline uptake was referred as adynamic bone disease.

Statistics

Statistical evaluation was carried out using currently available statistic software (SPSS). Mean ± SD for the different referring patients to our unit. Samples were allotted as follows: 94 concentrates; 50 reinfusates; 158 deionized water, groups were calculated. Differences among groups were obtained by analysis of variance or x2 test. When appropriate, and 71 dialysates. For the purpose of the present study, patients’ data were subdivided into three period groups: 1984–1987; 1988–1991; 1992–1995. In the case of dialysis fluids, because bone Al content may have been influenced by previous exposure, we also considered the 4-year-interval preceding our study (1980–1983).

Table 1. Mean values of serum, bone Al and mean Al(OH)3 consumption in the three periods considered in our dialysis patients

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>28</td>
<td>53</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Basal Al (μg/l)</td>
<td>42.7 ± 34.1</td>
<td>24.8 ± 21.9*</td>
<td>38.9 ± 34.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Delta Al (μg/l)</td>
<td>136.5 ± 105.7</td>
<td>98.7 ± 91.7</td>
<td>106.1 ± 96.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Al(OH)3 (g/day)</td>
<td>2.4 ± 1.6</td>
<td>2.1 ± 1.9</td>
<td>2.6 ± 2.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Al(OH)3 (total kg)</td>
<td>4.1 ± 2.9</td>
<td>4.0 ± 4.6</td>
<td>5.8 ± 7.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Bone Al (mg/kg/dw)</td>
<td>60.7 ± 43</td>
<td>29.0 ± 24.4*</td>
<td>31.9 ± 29.9*</td>
<td>0.00001</td>
</tr>
<tr>
<td>Aluminon positive (n)</td>
<td>7/28</td>
<td>1/53</td>
<td>0/36</td>
<td>0.001 ($)</td>
</tr>
<tr>
<td>ARBD (n)</td>
<td>2/28</td>
<td>0/53</td>
<td>0/36</td>
<td>0.03 ($)</td>
</tr>
</tbody>
</table>

ARBD, Al-related bone disease; (*) Bonferroni test: P < 0.05 as compared to 1984–1987; ($) x2 test.
Bone aluminium in dialysis: relative role of enteral and parenteral exposure

Table 2. Mean values (µg/l, ±SD) of Al content in several fluids employed for dialysis. A significant reduction of Al concentration is evident since 1984

<table>
<thead>
<tr>
<th>Years</th>
<th>Concentrates</th>
<th>Reinfusates</th>
<th>Deionized</th>
<th>Dialysates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980–1983</td>
<td>186.1 ± 98.0</td>
<td>22.0 ± 8.1</td>
<td>8.1 ± 5.0</td>
<td>26.1 ± 14.0</td>
</tr>
<tr>
<td>1984–1987</td>
<td>41.9 ± 15.0*</td>
<td>7.0 ± 4.0*</td>
<td>4.0 ± 2.0*</td>
<td>9.0 ± 6.0*</td>
</tr>
<tr>
<td>1988–1991</td>
<td>19.8 ± 4.1*</td>
<td>7.1 ± 3.0*</td>
<td>2.2 ± 1.0*</td>
<td>4.9 ± 2.1*</td>
</tr>
<tr>
<td>1992–1995</td>
<td>20.0 ± 3.5*</td>
<td>6.9 ± 3.1*</td>
<td>2.0 ± 1.2*</td>
<td>5.0 ± 2.0*</td>
</tr>
<tr>
<td>ANOVA</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
</tbody>
</table>

(*) Bonferroni test: P < 0.05 as compared to 1980–1983.

Bone Al content showed a clear halving of mean values (from 60.7 ± 43 to 29.0 ± 24.4 and 31.9 ± 29.9 mg/kg/dw, P < 0.00001) after 1987. The complete disappearance of Aluminium-positive cases in more recent years was also noted. In the three observation periods, the distribution of histopathological diagnoses changed as follows: adynamic bone disease from 0 to 5.6, to 8.3% (P = n.s.); osteomalacia from 7.1 to 3.7, to 5.5% (P = n.s.); mixed osteodystrophy from 71.4 to 33.9, to 44.4% (χ² = 10.3; P < 0.006); prevailing hyperparathyroidism from 21.4 to 52.8, to 41.6% (χ² = 7.4, P < 0.02).

As for ARBD, according to the diagnostic criteria suggested by Nebeker et al. [13], we could recognize only two positive cases in 1984–1987 (7.1%) and none in the following years (χ² = 6.4; P < 0.03).

Data of mean Al content in dialysis fluids in the different periods examined showed a significant reduction of Al concentration in all types of fluids employed, starting from 1984 (Table 2). In particular, Al content of concentrate fluids (186.1 ± 98.0 vs 41.9 ± 15.0 vs 19.8 ± 4.1 and vs 20.0 ± 3.5 µg/l respectively in the four periods considered; P < 0.0001) and, to a lesser degree, of reinfusates (22.0 ± 8.1 vs 7.0 ± 4.0 vs 7.1 ± 3.0 and vs 6.9 ± 3.1; P < 0.0001) was significantly reduced by the manufacturers. Al content in deionized water has always been acceptable (8.1 ± 5.0 vs 4.0 ± 2.0 vs 2.2 ± 1.0 and vs 2.0 ± 1.2 µg/l; P < 0.0001), but in the last 10 years is definitely safe. As a result, Al concentration in dialysate averaged 26.1 ± 14.0 µg/l in 1980–1983, decreased to 9.0 ± 6.0 µg/l subsequently, and reached unequivocally safe values following 1988 (4.9 ± 2.1 and 5.0 ± 2.0 µg/l; P < 0.0001).

Discussion

With the aim of reducing Al accumulation in dialysis, both parenteral and enteral exposure have been significantly reduced. However, while dialysate exposure may be easily controlled, a certain degree of intestinal absorption is often unavoidable [14]. The epidemic appearance of Al-related disease secondary to an accidental parenteral exposure through dialysate has also been recently described [15], but is expected to disappear rapidly. On the contrary the relative impact of more subtle changes in the two different routes of exposure to Al, which might have occurred following the increased attention paid to the problem of Al, has not been widely explored.

In our patients, over the time periods considered, a substantial stability of mean serum Al levels along with a constant oral intake, were recorded. In the general dialysis population, the percentage of patients who are prescribed an aluminium-hydroxide-containing drug has certainly decreased, but in a selected population like the one in our study, the mean daily dose was substantially unchanged in comparison with previous periods. Therefore the cumulative dosage was stable, but may increase as a consequence of the improvement in the patients survival rate. In this respect, bone Al content was markedly reduced.

Data of Al content in dialysis fluids show that patients of the period 1984–1987, who had the highest values of bone Al content, were being treated with fluids containing acceptable amounts of Al, while in previous years (1980–1983) they had been parenterally exposed to significantly greater amounts of the element.

In fact starting from 1988, probably following the EC resolution [16], an accurate control of Al in all dialysis fluids has been accomplished. Therefore, in our study the major reduction of bone Al accumulation observed after 1988 must be almost exclusively related to the reduction of exposure via dialysis fluids.

The persistence of a relatively high-dose prescription of Al hydroxide in our patients, could be explained by changes in the patients’ characteristics. As a matter of fact we have recorded a clear increment of cases with prevailing pure hyperparathyroidism (from 21.4% to 52.8% and 41.6% respectively; P < 0.02), i.e. of cases who generally have higher levels of serum PTH and phosphate [17] and which therefore might require a more aggressive oral phosphate chelation therapy.

In conclusion, despite the persistence of oral exposure to Al, a definite reduction of bone Al content has occurred in our dialysis population, and ARBD has completely disappeared. This result can be essentially attributed to the optimal control of Al content in dialysis fluids, which is therefore confirmed as a major factor for Al intoxication. Therefore it seems mandatory that Al concentration in dialysate be kept well below 10 µg/l. If this is accomplished, the only residual route for accumulation of Al in bone and other tissues would nowadays be the prolonged enteral administration of Al(OH)₃.

References


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