Low-dose (5 mg/kg) desferrioxamine treatment in acutely aluminium-intoxicated haemodialysis patients using two drug administration schedules

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Abstract

Background. According to the recommendations proposed at The Consensus Conference on Diagnosis and Treatment of Aluminium Overload in End-Stage Renal Failure Patients, Paris, 1992 low-dose desferrioxamine (DFO) treatment was applied for the first time in 41 acutely aluminium-intoxicated patients.

Methods and results. DFO-related neurological/ophthalmological side-effects were observed in nine of 11 patients with a post-DFO serum aluminium level > 300 µg/litre and in two patients below this level after a single administration of a 5-mg/kg dose of the chelator in the conventional way (i.e. the last hour of a dialysis session). They were no longer observed after introducing an alternative DFO administration schedule (i.e. administration of the chelator 5 h prior to the start of a haemodialysis session; group I: n = 14). A significant decrease in the serum aluminium levels as well as in the post-DFO serum aluminium increment (∆AsAl) was observed during the first 6 months’ course of low-dose DFO treatment in group I as well as group II (which consisted of patients receiving DFO in the conventional way; n = 27). Low-dose DFO treatment was accompanied by a significant increase in the mean ±SD serum iPTH levels (group I: 174 ± 245 up to 286 ± 285 ng/litre; group II: 206 ± 272 up to 409 ± 424 ng/litre; P < 0.005) and the mean corpuscular volume (group I: 80 ± 6.4 up to 85 ± 3.7 FL; P < 0.005; group II: 76 ± 5.0 up to 87 ± 4.3 FL; P < 0.0001). Serum ferritin levels significantly decreased in both groups. No further side-effects were observed during the DFO course. Patients in which DFO treatment could be stopped (i.e. subjects in which both serum aluminium and ∆AsAl were below 50 µg/litre at two successive occasions) before the end of the 6-months’ treatment course had a significantly greater residual diuresis (700 ± 682 ml/min vs 84 ± 109 ml/24 h). Also, residual diuresis was found to protect against aluminium intoxication as reflected by the values noted in group I versus those in group II.

Conclusion. The 5-mg/kg DFO treatment provides a safe and adequate therapy for aluminium overload. In severely aluminium-intoxicated patients presenting post-DFO serum aluminium levels above 300 µg/litre DFO should be given once weekly 5 h prior to high-extraction dialysis ensuring (i) maximal chelation of aluminium (ii) limited exposure to circulating desferrioxamine levels, and (iii) adequate removal of the latter compound. Finally, the necessity for a better communication between the local water distribution companies and the dialysis centres is a major lesson that can be drawn from this dramatic intoxication.

Key words: desferrioxamine; aluminium intoxication; acute; administration schedule; treatment

Introduction

In 1972 Alfrey et al. described for the first time a neurological picture associated with chronic haemodialysis [1] the so-called dialysis encephalopathy. This progressive encephalopathic syndrome was exclusively found among end-stage renal failure patients undergoing haemodialysis [2–4]. It was only in 1976, however, that the disease was associated with aluminium overload [5,6]. Before the introduction of desferrioxamine (DFO) as an aluminium chelating agent in 1980 [7] dialysis encephalopathy was almost invariably fatal [8–10]. From that time on the beneficial effects of DFO in the treatment of aluminium-related disorders have repeatedly been reported [11–16].

The most common sources for aluminium overload/intoxication in dialysis patients are the use of aluminium-contaminated dialysis and parenteral fluids and the prolonged ingestion of aluminium-containing phosphate binders [17,18]. During the last decade the potential risk for aluminium intoxication in dialysis patients has been substantially reduced by the partial
replacement of aluminium hydroxide by aluminium-free phosphate binders, the introduction of adequate reverse osmosis (RO) systems for water treatment, and by the development of routine methods for the regular monitoring of aluminium levels in serum, water and dialysis fluids [19,20]. Hence the 'classic' clinical picture of the epidemic and devastating acute aluminium intoxication expressed by encephalopathy and bone fractures [5,21–25] is now rarely seen. At present aluminium toxicity is mainly related to chronic low-level aluminium accumulation interfering with bone turnover, parathyroid hormone secretion, anaemia, and resistance to erythropoietin therapy [26,27]. Nevertheless acute aluminium intoxications may still occur and have been documented in several countries over the last 5 years in the context of our monitoring programme [25].

The scarce rainfall in the South of Portugal during recent years resulted in a subsequent decrease in the level of the water sources, resulting in high concentrations of suspended particles, which in turn necessitated the addition of huge amounts of aluminium sulphate as a flocculating/coagulating agent. This action was not reported by the municipal authorities. The passage of this severely contaminated water through the water-purification installation of a haemodialysis centre resulted in the obstruction of the cartridge filters and malfunction of the RO membranes. Finally, insufficiently treated water was sent to the dialysis machines and to the patients. This resulted in an acute aluminium intoxication manifested by the epidemic appearance of encephalopathy and microcytic anaemia [25].

Until recently [26] there was no consensus on dose, route of administration, frequency, and duration of DFO therapy. In order to reduce the risk for the various side-effects [28–31] that have repeatedly been reported in dialysis patients undergoing DFO treatment it was proposed at the Consensus Conference, Paris [26] to reduce the dose to 5 mg/kg in the treatment of aluminium overload. As previously noted the aluminium chelation capacity of this dose is not significantly inferior to the currently administered 30–80 mg/kg doses [32].

Here we report the results of the first 6 months low-dose DFO treatment course in 41 acutely intoxicated patients to which 5 mg/kg DFO was administered by either the conventional or an alternative administration schedule.

Subjects and methods

Patients

At the appearance of the first neurological symptoms in the concerned dialysis unit and the subsequent diagnosis of acute aluminium intoxication 71 patients were on haemodialysis treatment. Within 2 weeks, 11 patients had died. Another 14 critically ill patients were transferred to the intensive care unit of the Santa Cruz Hospital in Lisboa, Portugal. Forty-one acutely intoxicated patients in which no major encephalopathic manifestations (coma or convulsive activity) were observed were enrolled in a 6-month low-dose DFO treatment course according to a protocol recently proposed at the Consensus Conference [26]. Before starting DFO treatment all patients were informed individually and the protocol was outlined in detail. All patients gave a written informed consent conforming to the declaration of Helsinki.

Procedures

Pre-DFO initial treatment period. At the appearance of the first symptoms of acute aluminium intoxication a new RO system was installed and an alternative water source was used. The use of aluminium-containing phosphate binders was promptly stopped and replaced by calcium carbonate. The patients were followed intensively. Serum and dialysate aluminium levels were monitored every 2 weeks. Because of the patients' extremely high basal serum aluminium levels the first weeks after the intoxication (506 ± 253 μg/litre; range: 104–1257 μg/litre), DFO was not administered during this period in order not to increase the risk or worsen the patients' encephalopathic/ophthalmological state. Therefore the initial treatment consisted in six dialysis sessions (4 h)/week [5 days/week haemodialysis (HD); plus 1 day/week charcoal haemoperfusion/haemodialysis (HP/HD)] for 4 weeks. During the next 2 weeks, the frequency of the dialysis treatment was reduced to 2 days/week HD and 1 day/week HP/HD. Haemoperfusion was used since high-flux membranes known to have a comparable efficacy in the removal of aluminium [33] (and being much cheaper) were not available at the time of the intoxication. This treatment period will from now on be referred to as 'intensive HP/HD treatment without chelator'.

Initial low-dose DFO test. Before starting the DFO treatment protocol a low-dose 5 mg/kg DFO test was performed in all patients for evaluation of the degree of aluminium overload in each of the subjects. The DFO test was performed following a previously described protocol [34]. During the infusion time as well as during the 44 h post-DFO interdialytic period patients were under clinical surveillance. Particular attention was paid to the development of DFO-related neurological/ophthalmological side-effects or to worsening of the patients' neurological state. The DFO test was considered positive when the post-DFO serum aluminium increment (ΔsAl) was > 50 μg/litre [35]. Patients in which the DFO test was negative underwent a second test 2 weeks later. Desferrioxamine treatment was not initiated when both the basal serum aluminium and ΔsAl levels were below 60 and 50 μg/litre respectively; this was the case in five patients.

Low-dose DFO treatment. In total 41 patients underwent the low-dose DFO treatment course. Desferrioxamine was solubilized in 150 ml of a 5% dextrose solution in water. A 5 mg/kg dose was infused intravenously over 1 h once weekly. Patients were divided into two treatment groups according to the post-DFO serum aluminium values noted after the initial DFO test (which was performed 1 week prior to initiation of DFO treatment) and/or the presence of neurological symptoms.

In group I were included the patients (n = 14) presenting a post-DFO serum aluminium increment > 300 μg/litre and/or those in which the appearance or worsening of neurological or ophthalmological symptoms were observed following the initial DFO test. In this patient group DFO was infused in a peripherical vein 5 h before the start of the HP/HD session (Figure 1).

In group II were included all the patients (n = 27) having...
a post-DFO serum aluminium level <300 µg/litre in the absence of any neurological/ophthalmological symptoms. In these patients DFO was administered in the conventional way, i.e. infused in the venous blood line during the last hour of a HD session; aluminium was then removed by HP/HD 44 h later (Figure 1).

Initially 28 patients were included in group II. One patient however, could not tolerate HP treatment and after 2 weeks was transferred to group I. Within this group he was then treated by HP instead of HP/HD.

During DFO treatment patients underwent three dialysis sessions (4 h each) per week; one HP/HD following DFO administration, plus two HD. Data presented in this study were obtained in a first round-up made after 6 months of DFO treatment which consisted in a 4-month DFO course followed by a 1-month wash-out period and a second 2-month DFO treatment period.

Criteria to stop DFO treatment. DFO treatment was stopped when both the basal serum aluminium level and the post-DFO AsAl were below 60 and 50 µg/litre respectively at two successive (2-weekly interval) occasions. Treatment was also stopped in non-compliant patients (n = 1). During the treatment period one patient of group II died from hyperkalaemic cardiac arrest.

Determination of basal serum aluminium levels and DFO-test results. During the first 3 months of treatment basal serum aluminium levels were monitored every 2 weeks and monthly during the next months (Figure 2). Each month a DFO test was performed also. Serum samples were taken and aluminium determinations performed using the methodology previously described [36]. In addition to the serum aluminium levels, 'intact' PTH (iPTH; Nichols IRMA kit), total Ca, mean corpuscular volume (MCV), iron transferrin saturation, iron, and ferritin were measured before and at the end of the DFO treatment period.

HD and HD/HP procedures. Haemodialysis was performed using AK 10 Gambro® monitors equipped with a Cobe 400 cuprophane hollow-fibre dialyser (surface area: 1.0 m²). For HP/HD (performed in both patient groups once weekly during the first dialysis session following DFO administration) either an AluKart (amount of charcoal: 80 g; National Medical Care) or Adsorba 150 (amount of charcoal: 150 g; Gambro®) haemoperfusion column was inserted proximal to the dialyser [33].

Statistical analysis

The significance of the decrease of the patients' mean serum aluminium levels and post-DFO AsAl values in function of time was checked by the two-way ANOVA test for repeated measures followed by Bonferroni correction. Comparisons of the pre- vs post-DFO treatment values of a number of parameters such as the basal serum aluminium and post-DFO AsAl levels, iPTH, total calcium, iron, iron-transferrin saturation, ferritin, and MCV were made with the paired Student's t test. Differences between the two patient groups for these variables were analysed using the unpaired Student's t test. A P value <0.05 was considered significant at a two-tailed level.

Data are expressed as mean ± SD with exception of those presented in Figures 5 and 6, in which, because of the great biological variability of serum ferritin and serum iPTH values, SEM is used only for reasons of graphical layout.

Results

After the water treatment installation was replaced dialysate aluminium levels fell to below 2 µg/litre. This intervention in combination with the withdrawal of aluminium-containing phosphate binders resulted in a prompt decrease of the mean ± SD serum aluminium values from 506 ± 255 µg/litre down to 121 ± 46 µg/litre during the 6-weeks 'intensive HP/HD treatment period without chelator'.

A number of DFO-related side-effects were observed concomitantly with the initial 5 mg/kg DFO test (Table 1) when the chelator was given by the conventional procedure, i.e. administration during the last hour of a dialysis session followed by dialysis treatment 44 h later. Together with the post-DFO serum aluminium levels the presence of side-effects related to the DFO test were the base for patient grouping; i.e. group I, patients with a post-DFO serum aluminium level > 300 µg/litre and/or neurological/ophthalmological side-effects; group II, patients with a post-DFO serum aluminium level < 300 µg/litre without side-effects. Side-effects observed after the initial DFO test included both acute neurological and ophthalmological symptoms expressed by headache (n = 6), hallucinations (n = 2), myoclonic jerks (n = 1), and transitory blurred vision (n = 2). These were no longer observed after the chelator was administered by an alternative schedule consisting in DFO 5 h prior a dialysis session, and no other DFO-related side-effect were observed during the whole treatment course in the two treatment groups. As indicated in Table 2 presenting the clinical data of the patients included in both groups the mean residual diuresis in group II patients, i.e. the patients being less severely intoxicated, was significantly
Table 1. Post-DFO serum aluminium levels and DFO-related side-effects in patients of groups I and II after the 1st DFO test

<table>
<thead>
<tr>
<th>Group</th>
<th>Post-DFO sAl level (ug/litre)</th>
<th>Symptoms after initial DFO test (number of patients)</th>
<th>Patients without symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&gt; 300</td>
<td>Neurological (N = 7)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&lt; 300</td>
<td>Ophtalmological (N = 2)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>&lt; 300</td>
<td>Neurological (N = 2)</td>
<td>1*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abdominal cramps (N = 1)</td>
<td>26</td>
</tr>
</tbody>
</table>

*Patient who could not tolerate haemoperfusion (see also section 'patients').

Table 2. Clinical data of patients included in groups I and II

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I</th>
<th>Group II</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>54.8 ± 15.6</td>
<td>54.6 ± 15.2</td>
<td>NS</td>
</tr>
<tr>
<td>(range)</td>
<td>(29-84)</td>
<td>(27-78)</td>
<td></td>
</tr>
<tr>
<td>Time on dialysis, months</td>
<td>82.4 ± 41.1</td>
<td>55.8 ± 44.4</td>
<td>NS</td>
</tr>
<tr>
<td>(range)</td>
<td>(1-154)</td>
<td>(1-178)</td>
<td></td>
</tr>
<tr>
<td>Residual diuresis, ml/24 h</td>
<td>3.8 ± 13.3</td>
<td>304.8 ± 485.5</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>(range)</td>
<td>(0-50)</td>
<td>(0-2300)</td>
<td></td>
</tr>
</tbody>
</table>

(P < 0.05) higher as compared to the residual diuresis of the patients of group I.

(Bio-)chemical blood values in Table 3 demonstrate the significantly higher initial serum aluminium and AsAl levels in patients of group I vs those in group II (P < 0.05). During treatment a parallel, significant (P < 0.001) decrease of both the serum aluminium levels and AsAl values was noted in both groups (Figure 3 and Table 3).

Using the proposed criteria—basal serum aluminium < 60 μg/litre and AsAl < 50 μg/litre-low-dose DFO treatment could be stopped in eight patients of group II and two patients of group I within 6 months of treatment. The mean ± SD residual diuresis of the patients in which DFO treatment could be stopped prematurely was significantly (P < 0.001) higher (700 ± 762 ml/24 h) as compared to that of those (84 ± 139 ml/24 h) in which a second course had to be initiated.

After the low-dose DFO treatment course, MCV had significantly increased in both treatment groups (P < 0.005) (Figure 4). Interestingly, despite the dramatic decrease in serum aluminium values, in both treatment groups the MCV levels did not change during the intensive HP/HD treatment without chelator (Group I, 80.4 ± 7.8 fL (start) vs 79.5 ± 6.4 fL (end), NS; group II, 78.4 ± 5.7 fL (start) vs 76.2 ± 5.0 fL (end), NS). The iron-transferrin saturation remained unchanged during low-dose DFO treatment as were the serum iron levels. Serum ferritin values, however, showed a significant (P < 0.05) decrease in group I as well as in group II (Figure 5, Table 3).
Low-dose desferrioxamine in acute aluminium intoxication

MCV (lL)

Mean ± SD

Before After

Group I Group II

p<0.005 p<0.0001

Fig. 4. MCV values before and after 6 months low-dose DFO treatment course.

Ferritin ng/ml

Mean ± SEM

Before After

Group I Group II

p<0.005 p<0.005

Fig. 5. Serum ferritin values before and after 6 months low-dose DFO treatment course.

Furthermore a significant (P<0.005) increase in the serum iPTH levels was noted in groups I and II (Figure 6) during DFO treatment. As for MCV values, however, iPTH levels did not change during 'the intensive HP/HD treatment without chelator' (177±208 vs 185±244 ng/litre, NS).

Discussion

Although during the last decade the incidence and severity of aluminium-related diseases in end-stage renal failure, more particularly in dialysis patients, has markedly decreased, acute intoxications cannot be excluded even in the presence of RO-based water treatment systems and the limited use of aluminium-containing phosphate binders [25]. In the present study aluminium intoxication was due to malfunction of the cartridge filters which led to failure of the RO system to remove aluminium during the water treatment procedure. The efficiency of RO membranes relies on two rejection mechanisms: mechanical sieving and electrostatic interactions. By the latter mechanism the ionized aluminium will be eliminated efficiently (up to 99%) by the RO membrane, whereas colloidal aluminium is rejected by size exclusion of the RO membrane pores [37]. However, the unannounced addition of huge amounts of aluminium sulphate as a flocculating/coagulating agent into the water basins resulted in a high particle density which in the centre under study led to malfunction of the cartridge filters and consequent rapid fouling of the RO membrane, which in turn masked the electrostatic pulse mechanism, leading to an increased breakthrough of the aluminium. Here an effective layout of the water treatment system by for instance using two ROs in series or including double-bed deionization prior to RO might have been helpful in attaining a more adequate and safer water purification process. Note that with the latter deionizer type, which contains separate cation and anion columns, neutral colloidal aluminium particles become charged, allowing their removal by the cation exchanger [37].

The beneficial effects of DFO treatment—which at the present time is still the only available method to remove aluminium in dialysis patients—on reversal of the so-called aluminium-related diseases, i.e. aluminium-related bone disease [11,12], dialysis encephalopathy [13,14], and anaemia [15] and the improved response to erythropoietin therapy [16] are well known. In the past, however the chelator has been used in the presence of doses varying between 20 and 100 mg/kg [11–16]. With these doses several often fatal side-effects have been observed [28–31]. In order to reduce the risk for DFO-related complications the use of the 5-mg/kg dose was proposed recently at the Consensus Conference [26]. Using this dosage we previously dem-
demonstrated that sufficient chelation of aluminium occurs, whereas the levels of circulating ferrooxamine, being the agent responsible for the development of severe infections [31] are decreased dramatically [32]. The efficacy of the 5-mg/kg dose in long-term DFO treatment has not been demonstrated yet. Here it was applied in 41 acutely intoxicated dialysis patients. To reduce the risk for exacerbation of the patients' neurological state, chelation treatment was only started after basal serum aluminium levels had stabilized to below 200 μg/litre, which was achieved after 6 weeks of 'intensive HP/HD treatment without chelator'. During this treatment period HP was used, since high-flux membranes were not then available. Besides the fact that DFO is not recommended in patients with baseline serum aluminium levels above 200 μg/litre the rationale for using such high extraction devices in the absence of DFO is based on recent findings of our group [38], indicating that with extremely high serum aluminium levels as noted in the present study (up to > 1000 μg/litre) a considerable fraction of the element may appear non-protein bound. So in an attempt to accelerate the removal of this non-protein bound aluminium fraction in the absence of DFO 'intensive HP/HD treatment' was initiated, which was accompanied by a significant fall in the serum Al levels. In view of the dramatic context patients were to be treated in after the intoxication no additional studies on the dialytic removal of aluminium could be performed during this treatment period. Hence it cannot be deduced from our findings to what extent tissue deposition of the element has (beside the dialytic removal) contributed to the fall in serum aluminium levels observed during this period.

The risk of neurological side-effects was further reduced by giving the chelator according to two administration schedules, dependent on the patients' neurological state or serum aluminium levels following a low-dose DFO test. Even then, administering the chelator at a dose as low as 5 mg/kg in the conventional way, i.e. the last hour of a dialysis session after giving the chelator before dialysis. This indirectly indicates that with this strategy aluminium chelation was not completed at the start of the first dialysis after DFO, which is in agreement with previous data of our group showing maximal aluminium chelation to last at least 4 h. Therefore when administering the chelator prior to dialysis, limiting the exposure time to DFO and it's chelates will only be possible when chelation has been completed; in other words, Cmax levels have been reached at the start of the dialysis session following DFO, i.e. at least 4 hours after the end of DFO infusion.

Besides a significant decrease in both the serum aluminium and AsAl levels the efficacy of the low-dose DFO treatment is also demonstrated by the significant increase in the serum iPTH levels. This has repeatedly been demonstrated in previous reports using high (20-80 mg/kg) DFO doses in the treatment of aluminium-related bone disease [11-12] also. In the latter studies it was demonstrated that the removal of aluminium resulted in an increased parathyroid gland function, yielding an enhanced serum iPTH secretion, which in turn was accompanied by an improved bone histology/activity and a reduction in the stainable bone aluminium deposits. Our data showing serum calcium levels remaining stable during DFO treatment suggest a direct effect on the parathyroid gland, i.e. the removal of aluminium from this tissue rather than an increased iPTH secretion secondary to an increased calcium deposition in bone following the increased mineralization induced by the removal of aluminium from bone [41].

Using DFO doses of 40–50 mg/kg both an improvement of the anaemia [15] and an enhancement in the haematopoietic response to erythropoietin [16] have previously been reported. In the present study using the 5-mg/kg dose we noted a significant rise in MCV in both treatment groups. Interestingly there was an increase neither in MCV values nor the iPTH levels during 'the intensive HP/HD treatment without chelator', notwithstanding that a dramatic decrease of the serum aluminium levels was noted at that time. This observation suggests that in the absence of a DFO only the exchangeable aluminium pool and not the tissue aluminium is removed and that clinical improvement will only be achieved when one is able
to eliminate the element from its accumulation sites where it exerts its toxic action.

Serum ferritin levels decreased during low-dose DFO treatment whereas the iron-transferrin saturation remained unchanged. This observation is in agreement with previous findings indicating that DFO is able to chelate ferritin-bound iron [42]; however, it fails to remove iron from transferrin [43].

Patients with a significant residual diuresis seemed to be less severely intoxicated. This observation agrees well with the assumption made by Altmann et al. [44] that residual renal function protects against hyperaluminaemia. This residual renal function also contributes to the efficacy of DFO treatment, since it was highest in patients in which treatment could be stopped before the end of the DFO course.

In conclusion our data indicate that severe aluminium overload can adequately be treated using a DFO dose as low as 5 mg/kg. However, even with these doses neurological side-effects may occur unless exposure to circulating AIO or DFO is limited; a prerequisite which can be met adequately by administering the chelator 4–5 h prior to the dialysis session. Finally, the necessity for a better communication between the local water distribution companies and the dialysis centres is a major lesson that can be drawn from this dramatic intoxication. Based on the findings of the present study an updated version of the strategy for treatment of aluminium-overload (Figure 7) proposed at The Consensus Conference [26] is presented.

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