Diagnosis and treatment of aluminium bone disease

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Abstract. Aluminium accumulation in serum and tissues is a well-known complication in patients with chronic renal failure, and retention of the element in bone has been implicated in the pathogenesis of the so-called aluminium-related bone disease (ARBD). Regular serum aluminium monitoring remains mandatory to detect patients and centres at risk for aluminium intoxication. Early recognition of ARBD however requires a desferrioxamine (DFO) test in combination with a serum iPTH measurement. Definite diagnosis of ARBD is made by histological examination of a bone biopsy. Once ARBD has been identified DFO treatment should be initiated and all potential sources of aluminium exposure eliminated. In order to minimize the risk for DFO-related cerebral, auditory and visual side-effects, and siderophore-mediated opportunistic infections the chelator should be used at low doses (5 mg/kg) and administered widely spaced (once weekly) following well-defined strategies of administration.

Key words: aluminium; aluminium-related bone disease; desferrioxamine; diagnosis; treatment

Introduction

The protective mechanisms against aluminium accumulation (renal excretion and the gastrointestinal barrier) are either absent in dialysis patients or are highly challenged by the intake of pharmacological doses of aluminium salts for the purpose of enteral phosphorus binding [1]. The clinical consequences of aluminium overload in these patients include a neurological syndrome, disorders of the hematological system and the development of the so-called aluminium-related bone disease (ARBD) [2]. The use of deionizers and reverse osmosis (RO) filters for water purification and the replacement of Al(OH)₃ by calcium-containing phosphate binding agents have markedly reduced the incidence and severity of aluminium-related diseases. However, despite the availability of modern dialysis treatment modalities, acute intoxications cannot be excluded [3]. Major concern is now focused on more subtle disorders involving the parathyroid glands, erythropoiesis and resistance to erythropoietin therapy. Recent data indicate that pure aluminium-related bone lesions such as vitamin D-resistant osteomalacia are now much less common, but that a notable proportion of patients still show evidence of aluminium deposition in bone. In addition to the classic vitamin D-resistant osteomalacia, bone aluminium deposition has been associated with the development of an adynamic bone disease characterized by a defect in matrix synthesis and a mixed lesion showing the histological features of both osteomalacia and hyperparathyroid bone disease.

Data in the literature on the value of serum aluminium monitoring and the use of the desferrioxamine (DFO) test for the diagnosis of aluminium overload/ARBD are controversial. This is mainly due to inaccuracies in the complex aluminium determination [4] and the lack of standardized protocols for dose and way of administration of the chelator. At the present time DFO is still the only available method for the treatment of ARBD. However, with the conventional doses and administration schedules, DFO treatment often has a number of side effects, infections with non-siderophore-producing germs being the most severe ones [5]. Here we present recent data on the value of serum aluminium monitoring and on the use of low DFO doses (5 mg/kg) in both the diagnosis and treatment of aluminium overload with particular reference to ARBD.

Diagnosis of aluminium overload/toxicity in dialysis patients

Clinical/biochemical manifestations of ARBD

ARBD is clinically manifested by symptoms of severe and diffuse bone pain, muscle weakness (especially upper legs) and spontaneous fractures. Laboratory findings include slightly elevated calcium values, which may increase dramatically after vitamin D administration. Serum iPTH hormone in general is low for the degree of renal failure whereas the serum alkaline phosphatase concentration is normal. In patients with
ARBD hypercalcaemia may persist after parathyroidectomy [6].

**Bone biopsy**

Histological, histochemical, and chemical bone biopsy examination must still be considered as the 'gold standard' for the diagnosis of ARBD. The most common types of histological aluminium-related bone abnormalities are the so-called 'pure osteomalacia' and 'adynamic bone disease'. Distinct features of aluminium-induced osteomalacia include extensive accumulation of the element at the mineralization front, a decreased number of osteoblasts and osteoclasts, increased osteoid volume and a marked decrease of double tetracycline-labelled surfaces. Sometimes increased osteoid width is not seen which is consistent with a picture of 'adynamic bone disease'. In many biopsies a mixed lesion is seen with features of both hyperparathyroid bone disease and aluminium toxicity. Aluminium deposition at the calcified bone boundary has also been noted in the presence of histological features of mild lesion, normal bone and even osteitis fibrosa [7,8].

Based on the most recent data in the literature, one may consider ARBD to be present when the aluminium stain covers more than 15% of the trabecular surface, and the bone formation rate is reduced to less than the lower limit of normal, e.g. 220 μm²/mm²/day [8,9]. Because the aluminium stain is not specific for aluminium, false positives can be observed if there is marked iron overload, a condition which is readily excluded by staining for iron. When the staining technique is combined with measurement of the bone aluminium content one will be able to detect patients with distinct 'aluminium overload' in the absence of the element's toxic effects; that is patients with elevated bone aluminium content (> 15 μg/g) and no (0%) staining for aluminium at the mineralization front (see below).

**Serum aluminium monitoring**

Bone biopsy is an invasive procedure that can only be performed by trained medical staff. Moreover, histological, histochemical, and chemical examination and interpretation are complex. Thus, reliance on bone biopsy for the routine diagnosis of ARBD is impractical. Among the non-invasive diagnostic tools available, regular monitoring of serum aluminium ranks as the easiest and most cost-effective. The determination of baseline serum aluminium holds a certain diagnostic value; however it mainly reflects recent aluminium accumulation [12]. In view of this one should not rely on a simple baseline serum aluminium determination to perform a bone biopsy or start therapy unless confirmation is provided by means of a DFO test.

**DFO test**

In some patients with serious bone aluminium deposition serum aluminium may be relatively low, particularly after withdrawal of Al(OH)₃ or when iron overload is present. DFO is a chelating compound that will liberate aluminium from its body stores causing aluminium-DFO complex, the so-called aluminoxamine, to enter the blood compartment from these sites. A substantial increment in the serum aluminium after DFO administration can point to the presence of ARBD. Data in the literature on the use of the DFO test are however conflicting. Many of these discrepancies must be ascribed to differences in doses, schedules of administration of the chelator, inaccuracies of the aluminium determination and cut-off levels used. Moreover, with the DFO doses used so far, varying between 30 and 80 mg/kg, serious side effects (see below) have been reported even after a single dose of the chelator. In view of this the use of low DFO doses (5 mg/kg) has recently been recommended at the Consensus Conference on Diagnosis and Treatment of Aluminium Overload in End-Stage Renal Failure; Paris, 1992. It has been shown that a distinct increase in the serum aluminium can still be observed after a 5 mg/kg DFO dose [13]. We recently demonstrated, by correlating DFO test results with bone biopsy findings of 77 dialysis patients, that the 5 mg/kg DFO test when combined with a serum iPTH measurement not only is useful to diagnose but also to differentiate between patients with (i) ARBD, (ii) increased risk for aluminium toxicity and (iii) aluminium overload. Here, subjects were considered aluminium overloaded when the bone aluminium content was >15 μg/g and/or a positive aluminium staining was observed at the bone calcification front (>0% of bone surface). Patients whose bone biopsy specimen showed a positive aluminium staining (>0%) independent of the type of bone lesion were considered to be at an increased risk for aluminium toxicity. ARBD was present when the bone biopsy revealed >15% positive staining for aluminium at the bone surface and the bone formation rate was below 220 μm²/mm²/day.

Using a ΔSAl (serum aluminium increment after DFO) cut-off value of 50 μg/l, the 5 mg/kg test had a
sensitivity of 91% and a specificity of 95% in the
detection of aluminium overload.

To detect patients at an increased risk for aluminium
toxicity the test had a high sensitivity (92%) but low
specificity (56%). In the population under study not a
single patient with a serum iPTH greater than 650 ng/l
presented a positive (>0%) aluminium staining. Hence,
by combining the 50 µg/l ΔSAI cut-off level with a
serum iPTH < 650 ng/l, a number of false positives
could be eliminated by which the specificity increased
up to 86%, resulting in acceptable positive and negative
predictive values.

Combination of the DFO test with a serum iPTH
value also resulted in an excellent diagnostic perform-
ance of the test in the detection of patients with ARBD.
Here the combination of a ΔSAI cut-off of > 50 µg/l with a
serum iPTH threshold < 150 ng/l resulted in a
sensitivity of 87% and a specificity of 95%, thus yielding
a Youden's index as high as 0.82. Using the Bayes'
theorem positive and negative predictive values of the
5 mg/kg test in function of the prevalence of the disease
are presented in Figure 1.

When using the DFO test in the diagnosis of aluminium
overload/toxicity, a well-standardized protocol
should be used. So, the chelator should be given during
the last hour of a dialysis session at the start of which
a serum sample is taken for aluminium determination.
A second serum sample is taken at the start of the
next dialysis session. ΔSAI is then calculated as the
difference between the two serum aluminium concen-
trations. With regard to the patients' follow-up and
treatment the above data indicate that a DFO test in
general is not necessary in patients with a serum iPTH
greater than 650 ng/l. In fact these patients may have
aluminium overload, however they are not prone to
the element's toxic effects since in these subjects the
element is not localized at the bone calcification front,
the critical site where aluminium exerts its toxic effect.

Within this group of patients the test should only be
performed when they are to be treated with vitamin D
or have to undergo parathyroidectomy, treatments
which may predispose to an increased risk for the
development of ARBD in the presence of increased
bone aluminium levels. Patients in whom a serum
iPTH < 650 ng/l is accompanied by a serum aluminium
> 30 ng/l on two successive occasions, and less than
this level in the presence of iron overload, should
undergo a low dose DFO test.

A strategy for the monitoring and diagnosis of
ARBD is presented in flow chart in Figure 2. Here the
decision to perform a bone biopsy for the final dia-
gnosis of ARBD in subjects with a positive DFO test
and a serum iPTH < 150 ng/l is left at the discretion
of the responsible nephrologist.

Treatment of aluminium overload/toxicity in
dialysis patients

Indications

With regard to the patients' follow-up, DFO treatment
in general is not necessary in patients with a serum
iPTH > 650 ng/l. Within this group, patients with
aluminium overload may benefit from early interven-
tion, e.g. withdrawal of aluminium-containing medica-
tion. In these subjects DFO treatment should only be
initiated in cases where vitamin D treatment has to be
started, parathyroidectomy be performed or there is
clinical evidence of neurological or hematological
manifestations of aluminium overload. In patients in
whom the serum iPTH varies between 150 and 650 ng/l
and the DFO test is positive, DFO treatment should be
postponed. Indeed within this group of patients one
cannot predict which of them will develop ARBD. In
these subjects the first line therapy should as a prevent-
ive measure consist in the withdrawal of all sources of
aluminium. Patients should be closely followed with
regard to the evolution of their serum iPTH and a
second DFO test performed in case serum iPTH has
decreased to less than 150 ng/l. Below this serum iPTH
patients with a positive DFO test are likely to have
developed ARBD. In these subjects and in those pre-
senting characteristic clinical symptoms related to alu-
minium accumulation (cerebral, bone, anaemia), low
dose DFO treatment should be initiated.

Procedure and strategy

The beneficial effects of DFO treatment—which at the
present time is the only available method to remove
aluminium in dialysis patients—on the reversal of

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**Predictive values of the low-dose DFO test in the diagnosis of ARBD**

<table>
<thead>
<tr>
<th>Serum iPTH &lt; 150 ng/l</th>
<th>ΔSAI &gt; 50 µg/L</th>
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<tbody>
<tr>
<td>Sensitivity: 87%</td>
<td>Specificity: 95%</td>
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Fig. 1. Predictive values of the low-dose DFO test in the diagnosis of ARBD (adapted from [9]).
aluminium-related diseases (dialysis encephalopathy, ARBD, anaemia and improved response to erythropoietin) are well known. In patients with ARBD DFO treatment will result in a significant decrease in the stainable surface bone aluminium, an increased number of osteoclasts and an increased bone formation rate [14]. With respect to biochemical parameters serum calcium is expected to decline, alkaline phosphatase and iPTH levels to increase, signs of hyperparathyroidism to increase and erythrocyte mean corpuscular volume and haematocrit to increase slightly.

Until recently the chelator has been used in the presence of doses varying between 20 and 100 mg/kg. With these doses, however, various often fatal side effects have been observed [5]. These include hypotension, exacerbation of aluminium-related encephalopathy, retinal and auditory neurotoxicity, and rash. DFO has been associated with the development of fatal
bacterial or fungal infections. Limited epidemiological studies have indicated a greater incidence of mucormycosis with higher doses and/or more frequent administration of the chelator, and shown that the growth of the fungi involved increases significantly in the presence of ferrioxamine, the iron chelate of DFO. Therefore, as for diagnosis, a low (5 mg/kg) DFO dose should also be used in the treatment of aluminium overload/ARBD. The efficacy of such a low dose was recently demonstrated in 41 severely aluminium-intoxicated dialysis patients [15]. In these patients a 6 month low-dose DFO course resulted in a marked decrease of baseline serum aluminium and ΔSAI. In addition, DFO treatment was accompanied by a significant increase in the mean serum iPTH and mean corpuscular volume, two indicators of treatment efficacy. Furthermore, in the latter study worsening of the patients' neurological symptoms, which was observed in subjects in whom the post DFO serum aluminium had increased to greater than 300 μg/l after administration of the chelator via the conventional way (i.e. during the last hour of dialysis followed by removal of the chelates 44 h later), was omitted by using an alternative DFO administration schedule, that is administration of the chelator 5 h prior to a dialysis session. Using the latter strategy maximal aluminium chelation is obtained whereas the exposure to circulating aluminoxamine, ferrioxamine or unchelated DFO is limited. With this alternative strategy for DFO administration no further side-effects were observed in the presence of a 5 mg/kg dose.

In the treatment of aluminium overload/ARBD the chelator should be administered once weekly during the last hour of dialysis in those patients in whom a preceding low-dose DFO test revealed serum aluminium not to increase to greater than 300 μg/l. In subjects with a post-DFO serum aluminium concentration above this level the chelator should be administered via the alternative schedule, i.e. 5 h prior to a dialysis session. Frequency of DFO administration should be limited to once weekly. Strategies for patient follow-up are presented in Figure 3.

The removal of aluminoxamine using conventional dialysers is modest, however it can be increased substantially by insertion of a charcoal haemoperfusion column or by replacing the conventional dialysers by high-flux polysulphone membranes [16]. With the latter devices up to 80% of both the aluminoxamine and ferrioxamine body burden can be removed during a single dialysis session. This not only provides a more adequate but also a safer DFO treatment.

Prevention of aluminium overload/ARBD

In practice, aluminium accumulation, and thus ARBD, cannot be totally prevented in uraemic patients. However, appropriate precautions can minimize the possibility of aluminium overload. Water used for preparing dialysis solutions, final dialysis fluids as well as the patients' serum aluminium levels should be monitored periodically. Efforts should be undertaken to keep aluminium levels in dialysis fluids below 3 or even 2 μg/l. Recently we demonstrated that dialysate aluminium levels as low as 9 μg/l may lead to a significant increase of the serum aluminium levels [17]. Administration of aluminium in any form to the patient groups identified as being at increased risk for aluminium toxicity (children, patients with diabetes, parathyroidectomized patients) should be avoided whenever possible. When aluminium is given concomitant ingestion of citrate in any form, including fruit juices and

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**Fig. 3. Strategy for low-dose DFO treatment (adapted from [15]).**
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effervescent analgesics, must be avoided. Replacement of Al(OH)₃ by calcium carbonate is a valuable alternative for phosphate binding. Unfortunately, for some patients, because of gastrointestinal intolerance or hypercalcaemia associated with calcium-containing agents, use of aluminium-containing phosphorus binders continues to be necessary.

Conclusions

Although extreme cases of ARBD expressed as vitamin D-resistant osteomalacia are now rarely seen in the dialysis population, a considerable number of patients still have increased bone aluminium levels as demonstrated by chemical bone analysis and surface aluminium staining. Moreover, there is always a risk for acute intoxications as repeatedly noted during our serum aluminium monitoring programme. Therefore water to prepare the dialysis fluids, dialysate and serum aluminium levels should regularly be checked to detect early patients and centres at risk for aluminium accumulation. When interpreting a patient’s serum aluminium level the iron status should be taken into account. In both the diagnosis and treatment of aluminium overload/ARBD DFO is still the method of choice, however the chelator should be used at low doses (5 mg/kg). When used to diagnose aluminium accumulation the DFO test should be used in combination with a serum iPTH measurement, yielding the opportunity to differentiate between the various degrees of aluminium overload. In the treatment of severely aluminium-intoxicated subjects (post-DFO serum aluminium level >300 µg/l) the chelator should be administered via an alternative schedule to further reduce the risk of DFO-related side effects. DFO should only be administered once weekly. Removal of the DFO chelates should be accelerated by using high performance extraction procedures.

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