DESFERRIOXAMINE-INDUCED CHANGES OF ALUMINIUM KINETICS DURING HAEMODIALYSIS

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Summary

The effects of desferrioxamine administration on aluminium kinetics during haemodialysis were studied. Desferrioxamine leads to an increase of plasma aluminium levels in patients on chronic haemodialysis which could be attributed to mobilisation of tissue aluminium. Furthermore the ultrafiltrable fraction of plasma aluminium was greatly enhanced thus increasing the effective concentration gradient of aluminium between plasma and dialysate. Desferrioxamine therefore leads to increased aluminium removal during haemodialysis and should be considered in the therapy of aluminium toxicity syndromes.

Introduction

High body burdens of aluminium (Al) have been frequently found in patients on chronic haemodialysis (HD) [1] and syndromes like dialysis dementia and fracturing osteodystrophy [2] have been attributed to aluminium toxicity. Based on the assumption that Al is strongly bound to plasma proteins the possibility of Al removal during HD has been denied [3] although it has been shown that Al can readily pass the dialyser [4]. In contrast, recent works from our group were able to demonstrate that Al is properly removable by HD [5] and that removal rate depends upon the concentration gradient between free diffusible plasma Al and dialysate Al. The report of Ackrill [6] showing a striking improvement of dialysis encephalopathy in a patient treated by desferrioxamine (DFA) prompted us to study Al kinetics during HD and compare it to our previously obtained results [5].

Patients and methods

Nineteen patients on long term chronic intermittent HD were studied. HD was performed three times per week for 6 hours each using hollow fibre artificial kid-
neys (CDAK 1.8 or 2.5, Cordis Dow, single pass). Throughout the study the patients were kept on constant \( \text{Al (OH)}_3 \) medication. Details of the methods of Al determination (using flameless atomic absorption spectrophotometry) have been published elsewhere [5]. Blood for Al determination was drawn from the dialyser blood supply lines (blood inflow line = bi, blood outflow line = bo). Ultrafiltrate was obtained by disconnecting the dialysate supply lines from the dialyser and applying negative pressure at the dialysate site. A plasma to ultrafiltrate creatinine ratio of 1 ascertained that ultrafiltrate was undiluted. Parallel to each study Al was measured in the dialysate.

Al kinetics were studied on the following occasions:

**Dialysis 1** Resembles our previous study [5] measuring Al kinetics during HD using a dialysate with an extremely low Al content (0.2 \( \mu \text{mol/L} \)). Measurements included estimation of Al at the beginning of HD at the bi and bo site of the dialyser as well as in plasma ultrafiltrate (UF) and at the dialyser bi site at the end of HD.

**Dialysis 2 – 5** were performed in sequence, the dialysate Al concentration being 1 \( \mu \text{mol/L} \). Kinetics were studied in a similar fashion as in dialysis 1.

**Desferrioxamine** (4g intravenously) was administered to all patients during the last hour of dialysis 3.

**Results**

**Plasma Al during HD at different dialysate Al concentrations (Figure 1)**

During dialysis 1 (low dialysate Al content) ultrafiltrable fraction of plasma Al was always higher than dialysate Al concentration thus producing a concentration gradient from the patient to the dialysate resulting in Al removal during HD in all patients.

Dialysis 2 (higher dialysate Al) shows the same principle of Al kinetics during HD. Only in patients whose free diffusible fraction of plasma Al was higher than 1 \( \mu \text{mol/L} \) (i.e. 20% of 5 \( \mu \text{mol/L} \)) was the concentration gradient directed towards the dialysate thus allowing Al removal during HD.

**Effects of DFA on predialytic plasma Al levels (Figure 2)**

Whereas the predialytic Al levels at the beginning of dialysis 2 and 3 were in the same range (not significantly different) there was a tremendous increase of Al levels at dialysis 4 (the dialysis following DFA administration). At the beginning of dialysis 5 Al levels returned to basic values as before DFA administration.
Figure 1. Behaviour of plasma Al (dialysate bi site) during HD at different dialysate Al concentration (dialysis 1 = 0.2 μmol/L, dialysis 2 = 1.0 μmol/L). a = at the beginning of HD, b = end of HD

Figure 2. Predialytic plasma Al levels at four sequential HD's (numbers 2, 3, 4 and 5 on abscissa denotes dialysis number). DFA (desferrioxamine) was administered during the last hour of dialysis 3
Figure 3. Mean plasma Al-levels (dialyser bi site at the beginning of HD) and distribution patterns of protein bound and free diffusible Al before (= dialysis 2) and after (= dialysis 4) DFA administration. Effective concentration gradient = eff $\Delta C$.

Figure 4. Behaviour of plasma Al during HD after DFA administration (dialysis 4). Open bars denote dialyser bi site, hatched bar denotes dialyser bo site; *** = $p < 0.001$. 

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Changes in protein binding of Al after DFA administration and its effect on the Al concentration gradient between patients and dialysate (Figure 3 and 4)

DFA administration increased the free diffusible Al fraction from normally 20% [5] to more than 30%. In combination with an increase in total plasma Al after DFA this resulted in a greatly enhanced effective concentration gradient between plasma Al and dialysate Al, thus facilitating removal of larger amounts of Al during HD. This finds its expression in an impressive decrease of Al levels during single dialyser passage as well as during the total 6 hours HD (Figure 4).

Discussion

In our previous study [5] we have shown that Al is dialysable and that Al removal during HD depends on the effective concentration gradient between plasma Al and dialysate Al. These findings are confirmed by the results of dialysis 2 showing that the same principles are valid at different dialysate Al concentrations.

The most striking feature of DFA administration was the subsequent increase of plasma Al levels, most probably due to mobilisation of tissue Al. Of additional importance are the alterations of plasma protein binding of Al after DFA administration. As free diffusible plasma Al rose from 20% to more than 30% suggesting a decrease of protein binding from 80% to about 70% there was a much higher proportion of total plasma Al available for Al removal during HD. DFA administration therefore resulted in an impressive increase of the effective concentration gradient between the free diffusible plasma Al and dialysate Al thus leading to enhanced Al removal during single dialyser passage as well as during the total 6 hours HD.

DFA is known to chelate iron in its trivalent ferric form. Earlier observations suggested that it is highly specific for iron without any effect on other trace metals including Al [7]. The findings of Ackrill [6] showing an improvement of dialysis encephalopathy and our results demonstrating striking alterations in Al kinetics during HD strongly suggest that DFA is able to chelate Al and that the Al-DFA complex can be readily removed by HD. DFA therefore should be considered in the therapy of Al-toxicity syndromes in patients on chronic HD.

References

Open Discussion

KLINKMANN (Rostock) What was the incidence of dialysis encephalopathy in your patients? Was aluminium administered to some of your patients just before starting dialysis treatment during the conservative period of treatment?

GRAF We have no patients with dialysis encephalopathy. The patients were studied after an overnight fast and they had no aluminium loading just before.

RITZ (Heidelberg) One source of concern to me is the pharmacokinetics of desferrioxamine in the anuric patient. Do you have any evidence about the metabolism of this compound which is normally cleared via the kidneys? Are there any potentially harmful effects expected if this is administered to anuric patients?

GRAF We have not seen any adverse effects of DFA administration.

KERR (Newcastle) When desferrioxamine is used to treat iron poisoning, more iron is removed than can be accounted for by urinary excretion and it is believed that some is excreted through the bowel. Do you have any evidence whether there is bowel excretion of the desferrioxamine-aluminium chelate? Have you looked at stool aluminium for instance?

GRAF We have not looked at the stool but we were not able to find significant iron in the ultrafiltrate, and we think that the major effect of desferrioxamine on iron is by bowel excretion. However we have not measured the aluminium nor iron in the stool.

FARRELL (Sydney) I was just curious as to whether or not you think that the desferrioxamine may be actually mobilising the aluminium from the gut, in which case that wouldn’t be going the right way.

GRAF Theoretically this is possible but we have not studied it yet.

DRÜEKE (Paris) There was one disturbing observation by a Parisian colleague, Dr Buisson in St Maurice Nephrology Centre near Paris who administered desferrioxamine to a haemodialysis patient having iron overload. He saw in this patient the acute occurrence of encephalopathy after administering desferrioxamine several times. So I want to ask you how many patients have you treated chronically and have you ever seen such an effect in acutely treated patients?

GRAF In this study DFA was administered only once without any adverse effect.

DRÜEKE You have shown on one slide that when treating your patient by desferrioxamine the protein-bound aluminium also goes up, not only the diffusible aluminium. How can you explain that?
GRAF The total plasma aluminium goes up due to tissue aluminium mobilisation. There is a rise in absolute protein-bound Al concentration but a decrease in percentage protein-bound Al.

DRÜEKE But is this desferrioxamine bound to protein or is it free in the plasma?

GRAF It must be free otherwise it would not be possible to pass the dialyser.

MERRILL (Chairman) Does desferrioxamine have any effect on the calcium?

GRAF We have not seen any effect on total plasma calcium values.