CONCOMITANT REMOVAL OF ALUMINIUM AND IRON BY
HAEMODIALYSIS AND HAEMOFILTRATION AFTER
DESFERRIOXAMINE INTRAVENOUS INFUSION

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Summary

In six anuric haemodialysed patients, aluminium and iron mass transfer were
determined 48 hours after 40 and 80mg/kg body weight desferrioxamine intrave-
nous infusion.

All patients were aluminium overloaded (mean ± SEM: 2.91 ± 1.05μmol/g
wet tissue bone) and two had high plasma ferritin. Haemodialysis and haemo-
filtration were performed using a highly permeable membrane.

The adequate dose of desferrioxamine for aluminium removal is 40mg/kg,
since aluminium mass transfer induced by haemodialysis and haemofiltration
(47.4 and 40μmol/session) are not significantly different from that obtained
with 80mg/kg.

Iron removal is dose related in high plasma ferritin concentration patients:
50 and 100μmol/session with haemodialysis and 29 and 175μmol/session with
haemofiltration after 40 and 80mg/kg body weight respectively.

Introduction

Desferrioxamine (DFO), a chelating agent of Iron (Fe) [1], is now currently
used in the treatment of aluminium (Al) overload [2–4], but, as yet, no clinical
studies have determined concomitant removal of Al and Fe by dialysis in Al
overloaded haemodialysed patients. We have, therefore, carried out a study of
the concomitant removal of Al and Fe by haemodialysis and haemofiltration
48 hours after DFO intravenous infusion with different doses (40 and 80mg/kg
body weight) in six Al overloaded haemodialysis patients.

Subjects and methods

Six patients (2 males, 4 females), mean age (± SEM) 46.7 ± 10.8 years (range
30–57 years) and mean weight 50.5 ± 7.7kg (range 38.5–60kg) with chronic
renal failure, on regular haemodialysis for 120 ± 14.3 months (range 77–156 months) were studied.

Aluminium hydroxide has been used in all patients for many years but was stopped three months before the study. Five patients had histological evidence of osteomalacia and one suffered from dialysis encephalopathy.

Mean Al content in bone biopsy was 2.91 ± 1.05µmol/g wet tissue (range 1.74–4.26µmol/g wet tissue).

Mean plasma ferritin concentration was 750 ± 384ng/ml (range 42–2100ng/ml), but only two patients had high plasma ferritin (1810 and 2100ng/ml respectively).

Haemodialysis was performed with a 150L dialysate batch and haemofiltration with a substitution fluid volume corresponding to one-third body weight, using in both cases a highly permeable membrane (Bio-Hospal 3000 S).

Dialysate Al concentration was less than 0.18µmol/L and dialysate Fe concentration was less than 0.35µmol/L in fresh dialysate and haemofiltration substitution fluids.

Desferrioxamine (Desferal-Ciba) was administered intravenously at different doses: 40 and 80mg/kg body weight, during 30 minutes after the end of a dialysis session, 48 hours prior to aluminium and iron removal.

Aluminium and iron were measured by inductively coupled plasma emission spectrometry [5] in plasma before (Pi) and after (Pf) each session, fresh (Di) and used dialysate (Df) substitution fluid (Si) and haemofiltrate (Ui). Mass transfer (N), extraction ratio (ER) and integrated clearance (ICI) were calculated according to the following formulae (V=volume, L/session):

1. Mass transfer: \(N \text{ (µmol/session)}\)

   \[
   \text{Haemodialysis: } \begin{align*}
   N_{\text{Al}} &= [(\text{Al}_{Df}V_{Df}) - (\text{Al}_{Di}V_{Di})] \\
   N_{\text{Fe}} &= [(\text{Fe}_{Df}V_{Df}) - (\text{Fe}_{Di}V_{Di})]
   \end{align*}
   
   \text{Haemofiltration: } \begin{align*}
   N_{\text{Al}} &= [(\text{Al}_{Uf}V_{Uf}) - (\text{Al}_{Si}V_{Si})] \\
   N_{\text{Fe}} &= [(\text{Fe}_{Uf}V_{Uf}) - (\text{Fe}_{Si}V_{Si})]
   \end{align*}
   \]

2. Extraction ratio: \(ER \text{ (per cent)}\)

   \[
   ER = 100 \left(1 - \frac{(\text{Al})_{Pf}}{(\text{Al})_{Pi}}\right)
   \]

3. Integrated clearance: \(ICI \text{ (ml/min)}\)

   \[
   ICI = \frac{N}{\frac{\text{Al}_{Pi} - \text{Al}_{Pf}}{\ln \text{ Al}_{Pi} - \ln \text{ Al}_{Pf}} T}
   \]

Student’s ‘t’ test was used in all statistical evaluations.

Results

Figure 1 shows mean Al mass transfer, extraction ratio and integrated clearance in the six patients, for haemodialysis and haemofiltration, 48 hours after intravenous infusion of 40 and 80mg/kg body weight.
Figure 1. Mean aluminium mass transfer, extraction and integrated clearance for haemodialysis and haemofiltration 48 hours after intravenous infusion of 40 (hatched column) and 80 (solid column) mg/kg body weight desferrioxamine.

Mean N(Al), ER(Al) and ICI(Al) are of the same order of magnitude and not significantly different for all DFO doses after haemodialysis or haemofiltration.

Table 1 lists mean iron mass transfer, initial plasma iron concentration and final plasma iron concentration in the six patients, for haemodialysis and haemofiltration, 48 hours after intravenous infusion of 40 and 80mg/kg body weight DFO.

Mean (Fe)Pi and Fe(Pf) are not significantly different for haemodialysis and haemofiltration in the high plasma ferritin group (1954ng/ml) and in the low plasma ferritin group (147ng/ml).

In addition, N(Fe) is dose related in high plasma ferritin concentration patients: 50 and 100μmol/session with haemodialysis and 29 and 175μmol/session with haemofiltration after 40 and 80mg/kg body weight respectively.
TABLE I. Mean iron mass transfer (N), initial (Fe)p_i and final (Fe)p_f plasma concentration for haemodialysis and haemofiltration 48 hours after intravenous infusion of 40 and 80mg/kg body weight desferrioxamine

<table>
<thead>
<tr>
<th>Mean plasma ferritin (ng/ml)</th>
<th>HAEMODIALYSIS</th>
<th>HAEMOFILTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DFO dose mg/kg/BW</td>
<td>(Fe)p_i μmol/L</td>
</tr>
<tr>
<td>1954 (n=2)</td>
<td>40</td>
<td>37.3</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>57.2</td>
</tr>
<tr>
<td>147 (n=4)</td>
<td>40</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>15.3</td>
</tr>
</tbody>
</table>

No side effects were observed after DFO intravenous infusion at any dose.

Discussion

To prevent loss of desferrioxamine by diffusion through highly permeable dialysis membranes it has been suggested infusing DFO at the end of the dialysis session, as there is a dramatic decrease in DFO half-life when it is infused during dialysis [6]. Our previous studies on aluminium and iron kinetics after DFO infusion have shown that 48 hours after infusion is the best time for performing Al and Fe removal by haemodialysis or haemofiltration [7]. Since the aluminium mass transfer obtained by haemodialysis or haemofiltration are not significantly different after 40 or 80mg/kg body weight DFO, haemodialysis 48 hours after 40mg/kg body weight DFO is suggested for Al removal. DFO-aluminium complex clearance is in the range of middle molecule clearance using highly permeable membranes, which is consistent with its molecular weight (600–700).

In patients with transplants who have Al accumulation, DFO infusion induces urinary excretion around 150μmol a day [4], which is three times the mass transfer obtained by a dialysis session. However, Keberle has reported in dog experiments that 75 per cent of injected DFO was excreted into the bile [8]. One could expect that between 300–500μmol of aluminium are excreted via the intestinal route after each DFO infusion.

Desferrioxamine infusion is an effective treatment for iron removal in patients with chronic anaemia who required repeated blood transfusions with the risk of long-term iron poisoning: average weekly iron excretion is 0.3–0.9mmol in urine and 2–4mmol in faeces [9,10].

Our study shows that after 80mg/kg body weight DFO intravenous infusion, 0.3–0.5mmol of iron could be removed weekly in high plasma ferritin patients which is similar to the weekly urinary iron excretion in subjects with normal renal function. Since desferrioxamine and its metabolites are mostly excreted via the intestinal route, quantification of Al and Fe output must take faecal excretion into account in aluminium and iron overloaded patients.
References

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Open Discussion

SHALDON (Chairman) Your observation on the faecal balance completing the total amount removed is interesting. Do you think there is a large variation from individual to individual in the amount of desferrioxamine that comes out via the gut as opposed to across the membrane?

CIANCIONI Yes. I think there is a large variation between patients with iron stores but the question is to evaluate iron stores in patients.

SHALDON If you have a normal iron store some people have recommended giving supplementary iron if you are using desferrioxamine for aluminium removal. Do you have any opinions on that?

CIANCIONI In our long-term experience of desferrioxamine we think that it is necessary to give iron to patients who are treated only for aluminium overload.

SHALDON So you would recommend in patients who are not iron overloaded routine intravenous iron supplements if on a long course of desferrioxamine?

CIANCIONI Yes, I think that is quite important.