DESFERRIOXAMINE TREATMENT FOR ALUMINIUM AND IRON OVERLOAD IN URAEMIC PATIENTS BY HAEMODIALYSIS OR HAEMOFILTRATION


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Summary

In an attempt to quantify iron and aluminium removal in patients following desferrioxamine therapy, a comparative study of haemodialysis and haemofiltration was performed in five patients. Haemofiltration was found to be the more efficient treatment especially if iron and aluminium clearances were related to urea clearances. The distribution volumes of chelated iron and aluminium at the low clearance rates obtained, behave as a single compartment which amounts to about 40 per cent of body weight.

Introduction

Desferrioxamine (DFO) treatment is increasingly used in end-stage renal disease to eliminate iron (Fe) and/or aluminium (Al) during haemodialysis (HD) [1–4]. The rationale is that DFO chelates Fe and Al, deposited in body stores, and that this soluble complex is then removed by diffusion through the dialysis membrane. This therapeutic principle is now frequently used in patients needing frequent blood transfusions over a prolonged period of time and suffering from clinical signs of haemosiderosis. The other major indication for DFO therapy is in chronic Al intoxication leading to specific osteopathy and/or encephalopathy [3,4]. Although this therapy is widely used only limited data is available about efficiency of removal in different forms of ESRD treatment. Therefore it is the purpose of this study to quantify Fe and Al removal during haemodialysis and haemofiltration (HF) and to relate it to urea clearances and to try to establish the distribution volumes of chelated Fe and Al.

Patients and methods

Five RDT patients (3 females, 2 males, age 25–64 years) who had been on haemodialysis for a mean of 5.9 years (2.8–8.5 years) entered the study. They all suffered from haemosiderosis. During the last 12 months a mean of 20.4
units of blood per patient were transfused because of different clinical requirements. In all cases plasma ferritin was elevated to a mean of 4,000μg/L (2,300–8,000μg/L). DFO (30mg/kg/BW) was given as infusion (IV) 48 hours before treatment. Then the same patients were treated with either haemodialysis or HF in a chance sequence of a one week time interval. Haemodialysis was performed at a QB of about 200ml/min and a QD of about 500ml/min for four hours using a 1.2m² cuprophan hollow fibre dialyser with a wall thickness of 11μm (GF 120M; Gambro). A four hours HF with a 1.6m² polyamide hollow fibre haemofilter (HF 202; Gambro) was performed at a maximal QB (>300ml/min) resulting in ultrafiltration rates of about 120ml/min. In addition to plasma, ultrafiltrate was harvested immediately before and after the dialysate by installing small ultrafilters with a polyamide membrane (UF1700; Gambro). During HF, ultrafiltrate was directly sampled from the haemofilter. Plasma and filtrate were taken every 30 minutes during the test treatments. The plasma, filtrate, and dialysate concentrations of urea, Fe and Al were measured, urea in a Beckman autoanalyser by the enzymatic conductivity rate method whereas Fe and Al were analysed in a flameless atomic absorption spectrometer (Perkin Elmer). Then from these concentrations, measured QB and QD, HCT and plasma protein concentration, whole blood and plasma water clearances were calculated. Distribution volumes (V) of urea and chelated Fe and Al were calculated:

\[ V = \frac{UF}{BW \cdot \ln \frac{Ct}{Co}} \]

UF is total ultrafiltrate volume during HF, BW is body weight and C represents plasma water concentrations at start (Co) and end of treatment (Ct).

Results

Forty-eight hours after infusion of DFO a significant increase in plasma concentration of Fe and Al was observed: Fe increased from a mean of 166 ± 75 to 307 ± 88μg/dl and Al from 99 to 237μg/dl. The total amount of Fe removed during haemodialysis and HF varied from patient to patient dependent on the initial plasma concentration. In the patients of this study amounts ranged from 2–17mg of Fe and between 1 and 4mg of Al per treatment. Average plasma Fe concentrations fell during haemodialysis by a mean of 16.5 per cent compared to 21.5 per cent during HF. The corresponding values for Al were 47.6 per cent for haemodialysis and 50.7 per cent during HF (Figure 1). Plasma urea concentrations decreased 65 per cent during haemodialysis and 57 per cent during HF. During the same trial runs plasma water concentrations of Fe fell during HD by 43 per cent and during HF by 59 per cent and for Al 43 per cent during haemodialysis but 64 per cent during HF (Figure 1). Plasma water urea concentrations fell by the same percentage as plasma concentration, 65 per cent during haemodialysis and 57 per cent during HF. From QB and plasma water concentration clearances during haemodialysis were calculated to be for urea 60 ± 17ml/min, Fe 58 ± 26ml/min and Al 80 ± 20ml/min. Knowing from in vitro studies that water soluble urea, chelated Fe and Al were filterable with a sieving coefficient of one the mean filtration rate was identical to clearance
rate for all three solutes (105 ± 21 ml/min). Although the absolute clearances for Fe and Al during HF were superior to those during haemodialysis, for practical purposes it seems to be logical to correlate it to the particular urea clearances (ClFe or ClAl/ClU). Calculating this for haemodialysis, the ratio is only 36 per cent for Fe and 50 per cent for Al in contrast to HF where both figures reach 100 per cent indicating that for a comparable urea clearance Fe and Al are far more efficiently removed by HF than by haemodialysis.

The intra-treatment concentration profiles for plasma water urea, Fe and Al concentrations fitted very well a semilogarithmic curve. From the high correlation coefficient for this semilogarithmic decay of 0.9994 for urea, 0.912 for Fe and 0.917 for Al it can be assumed that at least at these relatively low clearance...
rates distribution volumes for all three solutes behaved like a single compartment. Distribution volume of urea was 60 per cent of BW, that of Fe 44 per cent and of Al 38 per cent of BW.

Discussion

Treatment of choice of clinically evident haemosiderosis in ESRD patients should either be discontinuation of further Fe substitution or renal transplantation. Iron prescription can be stopped immediately but usually regular blood transfusions have to be continued because they are clinically mandatory to keep the patient alive. In these cases renal transplantation offers the best chance of curing haemosiderosis. Iron stores can eventually become depleted by repetitive plebotomy since patient’s haemopoetic function is normal after transplantation and high haematocrits are usual. Unfortunately only a minority of patients needing regular blood transfusion can be transplanted with an acceptable risk, because these patients are either older or they suffer not only from renal failure but also from secondary diseases, interfering with renal transplantation. For these patients DFO treatment has become the treatment of choice in clinically evident haemosiderosis [2]. In ESRD patients chelated Fe is either excreted into the faeces in rather limited amounts or it passes across the dialysis membrane during treatment [2]. Quantitative differences exist between the different membranes used in commercially available dialysers. In in vitro studies polyacrylonitrile membranes show a higher efficiency than cellulosic membranes and it can be expected the clearance will become even higher with membranes

![Figure 2](image)

Figure 2. Comparative clearances of iron (Fe), aluminium (Al) and urea (U) during haemodialysis (HD) and haemofiltration (HF). For operating conditions and explanations see text
of high hydraulic permeability [5]. From a therapeutic point of view convective
treatment modes should be superior to diffusive modalities since chelated Fe and
Al are filtered without restraint and in this regard behave like urea. In contrast
in haemodialysis the greater size of chelated Fe compared to urea explains the
differences in clearances. These theoretical considerations are confirmed by
results of this study (Figure 2).

Aluminium intoxication resulting in encephalopathy and/or osteomalacia is
also preferably treated by renal transplantation, but if this is not possible DFO
therapy is the treatment of choice [3,4]. The arguments used above for Fe in
regard to removal during diffusive or convective treatment modes also hold for
chelated Al as seen from Figure 2: As the amount removed during treatment is
determined by initial concentration, clearance rate and distribution volume we
tried to determine the distribution volume of chelated Fe and Al and to com-
pare it with urea distribution volume, an established measure for total body
water. From concentration decay curves it was estimated to about 40 per cent
BW for chelated Al. Whether it is possible to imagine the size of the Fe and Al
pool by measuring the increase in plasma water concentration following DFO
administration needs to be investigated. The increase in plasma water con-
centration, however, could be a more relevant clinical parameter if iron and alumi-
nium overload than the increase in plasma concentrations. The increases in plasma
water concentration might also help to find the correct DFO dose to mobilise
the optimal amount of Fe and Al from body stores.

References
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4 Plerides AM, Myli PM. Contr Nephrol 1984; 38: 65
5 Schmidt M, Baldamus CA, Schoeppe W. Blood Purification. In press

Open Discussion

KERR (Chairman) In one of your slides the ultrafiltrable aluminium was as
high as the total serum aluminium, was that a misconception on my part or is
that what you really showed. It seemed that the ultrafiltrable aluminium in the
highest patient was 400μg/L but the serum aluminium was also 400μg/L. Are
these results from different patients?

BALDAMUS Yes, they are from different patients.