VASCULAR STABILITY AND MIDDLE MOLECULES REMOVAL IN HYPERTONIC HAEMODIAFILTRATION

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Summary

Hypertonic haemodiafiltration is a simultaneous hypertonic (Δ 550, Na 275mEq/L) low volume (7.2 litres) haemofiltration and hypotonic (Δ 282) short time (180') haemodialysis. Reduction of the predialysis body pool of MM (~48 per cent) and small molecules (~33 per cent) was obtained. No relationship between vascular stability and MM removal was observed. However, a net UF of 20.5ml/min and a greater removal of solutes up to 1500 daltons mw were obtained with a three hours thrice weekly dialysis programme.

Introduction

Short dialysis cannot be considered an optimal treatment because of inadequate control of vascular stability and insufficient correction of acid-base status. However, this treatment has been generally accepted as routine because the proved advantages of short sessions were considered superior to the unproved advantages of greater removal of solutes especially middle molecules. Presently, thanks to better membrane engineering and a correct approach to fluid balance, potentially higher dialysis efficiency seems compatible with superior clinical tolerance without former problems such as dysequilibrium syndrome. Moreover, as the toxicity of all products of intermediate protein metabolism are potentially similar, the favouring of a proportionate removal of all retained solutes without favouring special groups of molecules seems justified.

Material and methods

Hypertonic haemodiafiltration (H HDF) consists of a simultaneous hypertonic (Δ 550 mOsm/kg), low volume (7.2 litres of replacing solution) short time (180') haemofiltration session and hypotonic haemodialysis (Δ 282mOsm/kg) [1].

In order to avoid high end-dialysis serum sodium, the sodium concentration
of the main haemofiltration solution (Sol. 1A) is reduced in the last 30' of treatment (Sol. 1B). The compositions are, respectively: Sol. 1A (mEq/L), Na 275, Cl 150, HCO₃ 125 (calculated Δ 550); Sol. 1B (mEq/L), Na 125, HCO₃ 125, Glucose 278 (calculated Δ 528); Hypotonic dialysis solution (mEq/L), Na 130, K 2, Ca 4, Mg 1.5, Cl 112.5, Acetate 25, Glucose 5.5 (Δ 282).

To evaluate the different effects on extraction of solutes from the tissues related to the high osmolality, the patients were acutely treated with isotonic solutions and solute removal compared. These solutions were: Sol. 2, Isotonic haemofiltrate (mEq/L), Na 140, K 2, Cl 114, HCO₃ 28, Glucose 7; Isotonic dialysis solution (mEq/L), Na 140, K 2, Ca 4, Mg 1, Cl 105, Acetate 40, Glucose 5.5.

Haemodiafiltration was also compared with standard haemofiltration (Sol. 2) and standard 1m² haemodialysis (isotonic) \( Q_B \) 300, \( Q_D \) 500.

The haemodiafiltration sessions were performed according to the following parameters:

- Duration: thrice weekly,
- Dialyser: Gambro Ultraflux 1.8m², \( Q_{Reinf} \) 40ml/min, \( Q_{UF} \) 61/55ml/min,
  \( Q_B \) 300, \( Q_D \) 500.

**Patients** Four anuric patients have been treated for up to eight months. The patients, clinically stable, were selected on the basis of an excessive interdialysis weight gain.

**Middle molecule separation** Sera and dialysates were first deproteinised by ultrafiltration through Diaflo XM50 membrane (nominal cut-off = 50,000 daltons) in Amicon cells (10ml) under nitrogen positive pressure = 3kg/cm². Five millilitres of sample + 5ml of saline were ultrafiltered until the residual was halved (5ml of the whole); the ultrafiltration was repeated four times, adding 5ml of saline each time, so that the final ultrafiltered volume was 20ml and the residual material 5ml.

Ultrafiltered material, resuspended in 5ml saline was subjected to a second ultrafiltration through a UM05 membrane (nominal cut-off = 500 daltons) following the procedures already reported. UM05 ultrafiltrate and residual materials were analysed by gel-chromatography on a Sephadex column G15 (Pharmacia) 2.6 × 50cm, after equilibration with ammonium bicarbonate buffer 0.02M at pH 8 at 0.75ml/min speed = 0.14ml/min cm² (peristaltic pump LKB Multiperplex). Eluates were continuously recorded and analysed by spectrophotometry at λ 254nm (Uvicord LKB 4700).

The chromatographic surface areas were calculated excluding the first peak related to molecular weight > 2000 daltons. Chromatograms of UM05 residual material are only related to substances with mw > 300, as 94 per cent of substances with mw < 300 are ultrafiltered through the UM05 membrane [2].

**Results**

The extraction index for urea and middle molecules was calculated from the following equation:
During the first eight months of treatment predialysis midweek body pool of solutes below a mw of 300 was compared with the predialysis pool of solutes between 300 and 1500 mw (Table I). The monthly reduction of the retained solutes was uninterrupted especially for middle molecules (mean monthly reduction: 6.8 per cent). The concentration of small molecules became stable sooner (Figure 1). The separate predialysis reduction was as shown in Table II.

In comparison with hypertonic haemodiafiltration the middle molecule removal of standard haemofiltration is only 79 per cent. In particular, the fractional hourly removal of middle molecules in hypertonic haemodiafiltration shows the following progression: 44.1 per cent (first hour), 27.4 per cent (second hour), 28.5 per cent (third hour) (Figure 2).

Clinical parameters are summarised in Figure 3. Despite the hypertonic infusion of sodium for 150', the serum sodium concentration rises from 141 ± 2 to 145 ± 2mEq/L and is easily normalised to 138 ± 3mEq/L during the last 30' of treatment. In fact, no significant interdialysis weight gain differences were found (+5.8 per cent versus + 5.4 per cent).

However, thanks to the stable high osmolality of the reinfusate, the average serum osmolalities show a reduction of only 3 per cent per hour. The substitution of hypertonic sodium with hypertonic glucose between 150' and 180' of treatment raises the glucose concentration from 5 to 15mMol/L. However, 60' after the end of dialysis blood sugar returns to within the normal range. Acid-base status is normalised (Table III).

Net ultrafiltration was increased from 14.9 ± 4 (HD) to 20.5 ± 4.8ml/min (H HDF). The frequency of the main intradialytic symptoms was 30 per cent during the last month of haemodialysis preceding the new treatment and dropped down to 11 per cent during the first month of hypertonic haemodiafiltration.
HYPERTONIC HAEMODIAFILTRATION
Long-term middle and small molecules changes

○ Predialysis midweek body pool of substances with m.w. >300 (<1500)
● Predialysis midweek body pool of substances with m.w. <300

Figure 1. The predialysis reduction of molecules below 300mw reaches the steady state (~33 per cent) soon. On the contrary the reduction of MM is uninterrupted up to seven months (monthly average ~6.8 per cent)
Fractional hourly removal of $>300<1500\text{mw}$ solutes in haemodiafiltration (HDF) and haemofiltration (HF)

Figure 2. During the first hour of treatment, hypertonic IV infusion increases the efficiency of solute removal in comparison to isotonic haemofiltration.
Figure 3
TABLE II. Haemodiafiltration versus haemodialysis mean predialysis reduction

<table>
<thead>
<tr>
<th>Molecular weight</th>
<th>Predialysis change</th>
<th>R</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 300</td>
<td>-33% (n = 8)</td>
<td>-0.829</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>&gt; 300 &lt; 1500</td>
<td>-47.9% (n = 6)</td>
<td>-0.953</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TABLE III. Acid-base status in haemodialysis (HD) and hypertonic haemodiafiltration (H HDF)

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th></th>
<th>Post</th>
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<tbody>
<tr>
<td></td>
<td>HD</td>
<td>H HDF</td>
<td>HD</td>
<td>H HDF</td>
</tr>
<tr>
<td>pH</td>
<td>7.30 ± 0.06</td>
<td>7.35 ± 0.05</td>
<td>7.40 ± 0.03</td>
<td>7.47 ± 0.02</td>
</tr>
<tr>
<td>pCO₂</td>
<td>31.6 ± 4.3</td>
<td>36.5 ± 2</td>
<td>34.5 ± 6.5</td>
<td>34.7 ± 2.9</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>15.4 ± 3.4</td>
<td>20 ± 2.3</td>
<td>21.8 ± 2.8</td>
<td>26.2 ± 1.6</td>
</tr>
</tbody>
</table>

However during the last month of observation it rose again to 30 per cent. Although change of dry body weight partially accounts for this event no relationship with the progressive reduction of MM was found.

Discussion

The use of an IV hypertonic infusion of sodium salts was motivated by the following reasons: it allows easy modulation of sodium infusion, offers a more reliable serum sodium concentration, allows a rapid change of the reinfusion bag in the last 30', thus avoiding a high end dialysis serum sodium and it corrects instantaneously unpredictable intradialytic hypotensive episodes by increasing the volume of the IV infusion. Moreover, the simultaneous association of dialysis treatment allows an easy separation of bicarbonate and calcium chloride and, through the reduction of the necessary volume of haemofiltration solution, increases the ratio of solute removal versus treatment cost.

Concerning clinical tolerance, the significant increase of net ultrafiltration and the limited change of interdialysis body weight, despite a transient rise in sodium concentration, confirms that this treatment fulfils the requirements for a treatment with few symptoms. The factors responsible for improved clinical tolerance are presently unknown. However, the association of a higher serum sodium, relatively stable serum osmolality, limited shift of potassium concentration

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mostly related to the correction of acid-base state cannot be easily achieved with standard short dialysis and thus may explain the present results.

Recently the removal of a destabilising factor of high molecular weight [3] has been reviewed as a possible explanation for the general improvement of clinical tolerance obtained in the course of haemofiltration. However, we could not verify any difference in terms of vascular stability between the first and the seventh month of H HDF, despite the progressive reduction of the body pool of middle molecules.

H HDF presents important differences in comparison with standard short dialysis. It has been shown, in fact, that patients treated for up to 10 years with the latter technique, show a progressive and highly significant retention of middle molecules [4]. H HDF appears to be superior to all present treatments we have tested. Moreover, long-term intermittent treatment provides a stable reduction of the body pool of MM, approaching, in our limited trial, 50 per cent of the base line values.

Finally, the fact that a large amount of solutes are removed during the first hours of treatment may be helpful in planning further reduction of dialysis sessions.

References


Open Discussion

LEWIS (Ulm, FRG) It is not clear to me why you have chosen to use the hyperosmotic method of haemodialfiltration. I can understand why you get improved clearance with haemodialfiltration compared with haemodialysis but your data does not seem to show whether the use of the hyperosmotic solution plays a role in improving clearances. Was this the objective in using the hyperosmotic method? Is it analogous to cell-wash dialysis?

CAMBI Actually the results showing improved removal of solute, especially of middle molecular weight, was unexpected until we realised that other trials performed with dialysis, especially by Stone in the USA, with a dialysate of 147 mEq, were able to remove over 40% of the intracellular compartment in comparison with standard dialysis. Because of that we had the suspicion that probably the distribution of solutes, especially of middle molecular weight, could be within the intracellular compartment. We were looking for a reduction of symptoms with a high sodium concentration. This was done intravenously just for pragmatic reasons and we found that the removal of solutes, especially of solutes of over 300 molecular weight, was highly significant. That means the next step will be an enquiry into the volume of distribution of these
solute and to the real reduction of the intracellular fluid compartment.

LEWIS Does this mean you have compared haemodiafiltration clearances directly with your special technique and found an improvement due to the high osmolality?

CAMBI The difference between 141 and 145 serum sodium concentrations was significant but we think the physiological range is enough to increase the removal of such solutes.

ANDREUCCI (Naples) I think patients are very sensitive to the reduction in dialysis time and Professor Cambi has reduced dialysis time to four hours three times a week, and now he is reducing it even more, to three hours, three times a week. What happens to the hypertension? Did you have patients with hypertension on haemodialysis or haemodiafiltration?

CAMBI Actually, any kind of manipulation of sodium concentration should be compatible with a neutral balance, otherwise the patient will become hypertensive. The sodium concentration did not go up too much and was totally corrected at the end of dialysis. We did not find a special correlation between fluid removal and hypertension. Only the patients who had a volume dependent type of hypertension were corrected, but the true hypertensive patients did not change.

DRÜEKE (Paris) I noticed that your infusion replacement fluid did not contain calcium. What was the effect of this on calcium and phosphate metabolism? Was there cellular phosphate depletion in your patients?

CAMBI No, actually the dialysate contained calcium at a concentration of 4 mEq/L. We did not find any change in the divalent ions in these patients and the serum calcium concentration did not change during dialysis.