HAEMOFILTRATION WITH SORBENT REGENERATION OF ULTRAFILTRATE: FIRST CLINICAL EXPERIENCE IN END STAGE RENAL DISEASE

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Summary

A sorbent system (Redy D11 cartridge) capable of 'in line' regeneration of ultrafiltrate during haemofiltration (Amicon 0.5 m²) has been developed and applied on 3 x 4 hr/week schedule to 3 patients with end stage renal failure previously treated for up to 6 months with haemodialysis. Total experience, to date, is 8 patient months. Tolerance to fluid removal improved with the new system. Patient well being and rehabilitation has been maintained. The system offers the potential of haemofiltration without sterile replacement fluid or expensive fluid balancing machines.

Introduction

The introduction of post-dilutional haemofiltration in 1976 [1], represented a technical advance over the original pre-dilution method of Henderson [2]. The reduction of the volume of sterile replacement fluid from 70 to 20 L per treatment and the development of an automatic system for continuously monitoring and controlling the fluid balance [3] permitted haemofiltration to become a 'clinical reality'. To date over 60 patients have been treated for at least 3 months and a few for as long as 3 years [1,4–6]. If the claims of improved blood pressure control and patient tolerance of fluid removal, together with an amelioration of hyperphosphataemia and hypertriglyceridaemia without drugs are confirmed, then this technique will have a definite place in the treatment of end stage renal failure. For these reasons, we have developed a technique of sorbent regeneration of ultrafiltrate (SRU) with its subsequent reinjection in a closed circuit to eliminate the need for sterile replacement fluid and expensive automated balancing equipment.

Methods

A conventional extracorporeal blood circuit consisting of an A-V fistula access
Figure 1. Flow diagram of sorbent regeneration of ultrafiltrate during haemofiltration
site, an Amicon 0.5 m² capillary haemofilter, roller blood pump, venous pressure monitor and ultrasonic air detector and venous clamp were used (Figure 1). Continuous heparinisation was employed using the same dose as for haemodialysis. The ultrafiltrate circuit consisted of a second roller pump which drew ultrafiltrate from the blood at a rate of 80–100 ml/min (provided blood flow was 250–300 ml/min and the transmembrane pressure was at least 300 mmHg). The detection of a rupture of the haemofilter membrane was monitored by an external blood leak detector. The ultrafiltrate flow rate was measured continuously by an in line ‘rising ball’ flow meter calibrated at 37°C. The fluid then passed through the sorbent cartridge (Redy D11 chloride cartridge pre-treated by rinsing it with 5 L 1/6 M NaHCO₃ for 30 min resulting in an uptake of about 150 mEq Na⁺ and HCO₃⁻ in exchange for H⁺ and Cl⁻ [7,8]). Before the cartridge, a third roller pump removed excess fluid into a graduated measuring cylinder, thus permitting precise control of patient’s weight loss during the procedure. At the exit from the cartridge, a solution of 5% glucose containing CaCl₂, MgCl₂ and KCl was infused at a constant rate (250 ml/hr) to replace these ions removed by zirconium phosphate in the cartridge. The ultrafiltrate was then rewarmed to 37°C and the CO₂ originating from the urease degradation of urea in the cartridge was removed in a 20 ml degassing chamber. The top of the chamber (surface area 6 cm²) was covered by a hydrophobic polypropylene membrane, which was permeable to gas but not to fluid. The bubble-free ultrafiltrate was then sterilised by passage through a second Amicon 0.5 m² filter, which also removed particulate matter (carbon emboli and aluminium oxide from the cartridge) and pyrogen, and finally re-entered the blood at the venous bubble trap (post-dilution). Blood and ultrafiltrate samples before and after the cartridge and after the sterilising filter were drawn at half-hourly intervals during 4 hr treatments on 9 occasions. Routine pre- and post-treatment samples were drawn weekly. Urea, creatinine, uric acid, phosphate and electrolytes were measured in plasma and ultrafiltrate by an autoanalyzer using routine methods. Osmolality was measured from depression of the freezing point with a Fiske osmometer. pH, CO₂ and derived bicarbonate were measured with 1 L autocal/613 blood gas analyser. Middle molecules, peak 7 and sub peaks were measured by high speed gel filtration followed by gradient elution chromatography [9].

Ultrafiltrate samples were cultured periodically and tested for presence of pyrogen by Limulus lysate assay. Particulate matter in the ultrafiltrate was also measured.

Intactness of the sterilising filter was checked before use by injection of dextran blue (MW 2 x 10⁶ dalton) into the capillaries. Failure to detect dextran blue in the filtrate was taken as evidence of the absence of any leakage in the filter [10].

**Material** (Table I)

Three unselected patients have been treated 3 x 4 hr/week for 2–3 months after informed consent had been obtained. One patient was previously treated for 3 months with conventional post dilution haemofiltration (20 L of infusion

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TABLE I. Clinical Experience with Haemofiltration and Sorbent Regeneration of Ultrafiltrate

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Wt (kg)</th>
<th>Creatinine Clearance (ml/min/l. 73m²)</th>
<th>Treatment Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.B.</td>
<td>F</td>
<td>46</td>
<td>80</td>
<td>0</td>
<td>HD 6, HF 3, SRU 3</td>
</tr>
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<td>J.L.</td>
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<td>44</td>
<td>51</td>
<td>0.2</td>
<td>29, –, 3</td>
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<tr>
<td>F.M.</td>
<td>F</td>
<td>70</td>
<td>62</td>
<td>0.7</td>
<td>11, –, 2</td>
</tr>
</tbody>
</table>

HD = Haemodialysis: Gambro optima 1 m² 3x5 hr/week
HF = Haemofiltration (post-dilution) RP₆ 3x20 L exchange/week
SRU = Haemofiltration with sorbent regeneration of ultrafiltrate. Amicon 0.5 m² 3x4 hr/week.

fluid containing 40 mEq/L acetate) 3 x week. All patients had previously been treated for at least 6 months by 3 x 5 hr/week Gambro Optima 1m² single pass haemodialysis. All patients were on an unrestricted protein intake (estimated at 1.1 g/kg body weight) and on moderate restriction of K⁺ and Na⁺. Aluminium hydroxide was prescribed for all patients. No change in diet or medicaments was made when the treatment was changed.

Results

Ultrafiltrate and Redy Cartridge

The Redy cartridge completely removed urea, creatinine, uric acid, phosphate, middle molecules, potassium, magnesium and calcium on all samples of ultrafiltrate examined after the cartridge during the 4 hr treatment period at flow rates of ultrafiltrate varying between 80–120 ml/min. No free NH₃ was detected in samples taken at the end of the procedure. The sieving coefficient of these molecules remained constant at 1.0 and thus the effective clearance rate of the closed circuit for these substances was identical to the ultrafiltration rate obtained with the haemofilter.

The bicarbonate treated D11 cartridge added approximately 10 mEq/L of HCO₃⁻ and Na⁺ to the ultrafiltrate leaving the cartridge. However, the result of adding K⁺, Mg²⁺ and Ca²⁺ in a volume of 250 ml/hr resulted in a 5% dilution of the ultrafiltrate returning to the patient (e.g. UF before cartridge HCO₃⁻ 17.0, Na⁺ 137 mEq/L; after cartridge HCO₃⁻ 27.0 mEq/L, Na⁺ 147 mEq/L; after dilution before reinjection HCO₃⁻ 26 mEq/L, Na⁺ 141 mEq/L). In addition, as 1 L of diluting fluid was given in 4 hr this was added to the volume of ultrafiltrate removed for weight loss control and thus patients were always in negative sodium balance. In addition, no patient complained of thirst or had excessive weight gain in the periods between treatments compared with haemodialysis in 7 patient months of treatment (100 procedures). Considerable quantities of CO₂
were produced by the cartridge. This gas was effectively removed by a polypropylene membrane in an ‘in line’ degassing chamber before the sterilising filter. The concentration of $K^+$, $Mg^{++}$ and $Ca^{++}$ in the ultrafiltrate before reinjection into the patient was maintained by a constant infusion (250 ml/hr). However, as the ultrafiltration rate varied by up to 15% during the treatment there were fluctuations in the concentration of these ions in the returning fluid; mean results with ranges were as follows: $K^+$ 2.0 (range 1.7–2.3) mEq/L, $Mg^{++}$ 1.5 (range 1.2–1.8) mEq/L and $Ca^{++}$ 3.25 (range 2.75–3.75) mEq/L.

The ultrafiltrate taken immediately after leaving the Amicon 0.5 m² haemofilter and just before re-entry to the blood after the sterilising filter was consistently sterile and free of pyrogen and particular matter. However, the ultrafiltrate leaving the Redy cartridge before the sterilising filter was contaminated with bacteria, pyrogen and carbon particles. Nevertheless, no patient experienced a febrile reaction during or after the procedure in over 100 treatments.

**Clinical**

The clinical condition of the patients after 3 months of uninterrupted treatment by sorbent regeneration remains extremely satisfactory. No untoward symptoms or signs have appeared and all 3 patients preferred this system to conventional haemodialysis as they felt less fatigued and appeared to find treatment more comfortable. Objectively, the incidence of symptomatic hypotension, nausea or cramps has been reduced by 50%. Two patients have stated they feel less thirsty and their interdialytic weight gain reflects this. Pretreatment blood pressure has not changed. Peripheral nerve conduction times have remained unchanged compared with haemodialysis and in 1 patient when compared with classical haemofiltration as well. (mean HD 42.0 ± 2.4 m/sec mean SRU 42.5 ± 3.7 m/sec), and there was no change in haematocrit (mean HD : 27.2 ± 2.4%, mean SRU : 26.5 ± 3.1%).

Pretreatment biochemical control (Table II) showed the expected rise in urea and creatinine when the mean of the last 4 weekly measurements on haemodialysis were compared with those obtained with haemofiltration with SRU obtained in the second months of treatment (allowing the first month for equilibration). There was no change in phosphate control, a significant improvement in serum bicarbonate and equal reduction in serum osmolality during treatment. Fasting pretreatment triglyceride levels which were not previously elevated on HD did not alter with SRU.

**Discussion**

Sorbent regeneration of ultrafiltrate has been suggested as a future possible improvement in haemofiltration [1]. However, apart from acute animal experiments [11,12], no other reports have been published on its use in patients. Our data suggests that this possibility is now a practical reality, although the duration of our experience is limited to 3 months in the individual patient. If the well being of our virtually anuric patients continues, it would suggest that the sorbent
TABLE II. Comparison of Biochemical Control between Haemodialysis and Haemofiltration with Sorbent Regeneration of Ultrafiltrate (mean of 4 determinations at weekly intervals after longest intertreatment period)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Urea (mg/100ml)</th>
<th>Creatinine (mg/100ml)</th>
<th>Phosphate (mg/100ml)</th>
<th>Bicarbonate (mEq/L)</th>
<th>Δ Osmolality (m.osm/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HD</td>
<td>SRU</td>
<td>HD</td>
<td>SRU</td>
<td>HD</td>
</tr>
<tr>
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<td>13.9</td>
<td>5.6</td>
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<tr>
<td>J.L.</td>
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<td>10.1</td>
<td>11.5</td>
<td>5.0</td>
</tr>
<tr>
<td>F.M.</td>
<td>140</td>
<td>160</td>
<td>10.0</td>
<td>10.9</td>
<td>4.5</td>
</tr>
</tbody>
</table>

HD = Haemodialysis 3x5 hr/week: Gambro Optima 1 m²
SRU = Haemofiltration with Sorbent Regeneration of Ultrafiltrate 3x4 hr/week. Amicon 0.5 m²

Δ Osmolality = fall in m.osm/kg of serum osmolality during treatment procedure.

The system is capable of adequately removing major uraemic toxins. We have shown that it is able to remove urea, creatinine, uric acid, phosphate and middle molecules. Further work will be necessary to evaluate its effect on removing proteins, hormone polypeptides and amino acids normally found in ultrafiltrate up to a molecular weight of 20000. The major inconvenience with the Redy cartridge is the uncertain method of obtaining base replacement and the problem of added sodium, in addition to the total removal of Ca\(^{++}\), Mg\(^{++}\) and K\(^{+}\), necessitating their replacement. The bicarbonate input comes partly from urea breakdown and partly from exchange of anions in the zirconium oxide, bicarbonate-rinsed anion exchange system. The yield of bicarbonate from urea has been calculated: 1 m mole urea generates 0.4 m mole HCO\(_3\)\(^{-}\) [7] and the Na\(^{+}\) exchange for NH\(_4\)\(^{+}\) generated from urea breakdown varies from 3–10 m moles/g urea [13]. Both these figures will depend to a certain extent on the ratio of H\(^{+}\) to Na\(^{+}\) in the zirconium phosphate layer and how this is modified by the preliminary NaHCO\(_3\) rinse. However, if one assumes a 30 g urea uptake during the treatment, this would result in the formation of 120 m moles HCO\(_3\)\(^{-}\) and 90 to 300 m moles Na\(^{+}\). We found 150 m moles HCO\(_3\)\(^{-}\) were taken up by the cartridge during NaHCO\(_3\) preliminary rinsing and hence the measured input of bicarbonate into the patient of 200 mEq is reasonable and resulted in improved correction of acidosis compared with haemodialysis or conventional haemofiltration. However, the addition of 200 mEq Na required that the ultrafiltrate removed for weight loss equalled at least 1.5 L in order to maintain sodium balance. This problem was resolved by adding at each treatment 1000 ml of an aqueous solution containing the Ca\(^{++}\), Mg\(^{++}\) and K\(^{+}\) ions to the ultrafiltrate before returning it to the patient, thereby ensuring the need to remove 1000 ml in addition to the patient’s weight gain. The absence of thirst and excessive weight gain between treatments in these patients suggests that adequate control of sodium balance has been obtained.

The success of the Amicon filter in producing particulate free, sterile, pyrogenic ultrafiltrate after the ultrafiltrate has been contaminated by the unsterile
Redy cartridge is most encouraging. Experience to date suggests that the life of these filters is at least 2 months (26 uses) provided they are back washed and resterilised between use. Thus, the addition of a second Amicon filter becomes economically feasible.

Our results confirm that fluid removal achieved in a controlled linear manner during conventional haemofiltration is less symptomatic than in haemodialysis [1,3], but this cannot be explained by the smaller or zero change in serum osmolality reported by Quellhorst [14], as we saw identical drops in osmolality during haemodialysis, classical haemofiltration (in one patient) and haemofiltration with sorbent regeneration.

Our experience is too small and short to comment on the failure of improvement in hyperphosphataemia. As only one patient had a moderate elevation of blood pressure, and the other two were normotensive, no conclusions can be drawn as yet relating to the possible control of blood pressure by haemofiltration with sorbent regeneration of ultrafiltrate.

The potential advantages of the system are that it permits haemofiltration without the need for sterile replacement fluid or an expensive fluid balancing system and yet permits linear controlled asymptomatic weight loss. Miniaturisation and improvement of the sorbent system should facilitate the development of a portable artificial kidney.

Acknowledgment

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References

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Open Discussion

FUCHS (Goettingen) Could you please give a comment on the sodium balance because from theoretical consideration one would expect a highly positive balance?

SHALDON If one particular patient as an example lost enough weight in terms of fluid we could maintain negative sodium balance, but this one particular patient required 3 to 4 litres of fluid removal for excess weight gain. With more experience in the system we found it necessary to compensate for this by using the infusion system of calcium, potassium and magnesium in a larger volume and in fact we infuse one litre of fluid during the 4 hour period which gives us an automatic ultrafiltration rate of at least 1.5 litres in the 4 hours treatment period. This has enabled us to maintain sodium balance. Much to our surprise with no explanation, purely observation, 2 patients have lost rather than increased, and their rate of weight gain has actually decreased. Serum sodium levels were not really altered.

GRAEFE (Munster) I wonder whether you might be able to explain the enhanced ultrafiltration tolerance in these patients. There does not seem to be any relation to osmolality.

SHALDON I think that the evidence for wider tolerance to ultrafiltration, which is a consistent finding amongst all workers in haemofiltration, whatever else they disagree about, does not have an explanation at the moment. It may be just slow flow dialysis, but I think it could be better linear control of ultrafiltration. I don’t think we have an answer but the observation is there.