Ultrafiltration for Middle Molecules in Uraemia

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Summary

An ultrafiltration system for the purification of toxic substances is demonstrated. Using this system, it is possible to eliminate substances with a molecular weight up to 5,000 in the same amount as smaller molecules. The clearances for smaller molecules are lower and for larger molecules higher compared to haemodialysis and they depend mainly on the ultrafiltrate flow. Amino acid loss did not exceed the amount which was eliminated by plate haemodialysers. Side effects, such as excessive haemolysis, platelet or fibrinogen depletion, were not to be found.

Introduction

According to Babb (1971), the symptoms of uraemia, especially abnormal nerve conductivity and anaemia, are due to an accumulation of toxic substances with a molecular weight of more than 1,000. As clinical experience shows, a retention of substances with a smaller molecular weight (e.g. urea and creatinine) is tolerated without the development of uraemic abnormalities. Since the investigations of Henderson (1970, 1973), ultrafiltration is expected to be more efficient in eliminating these ‘middle molecular’ substances than haemodialysis. The following investigations were performed in order to evaluate the ability of a blood ultrafiltration device to clear uraemic toxins and to detect any possible side effects.

METHOD

Blood ultrafiltration was performed using a plate ultrafilter consisting of cellulose nitrate membranes between supports of polycarbonate plastic. In order to avoid membrane polarisation, the blood flow, applied pressure and filtrate flow were perpendicularly orientated (Figure 1).

158
Figure 1. Perpendicular directions of blood flow and trans-membrane pressure, by which membrane polarisation is prevented.

Figure 2. Cellulose nitrate membrane (x 12,500 approx.).

Figure 2 shows an electron microscope photograph of a cellulose nitrate membrane. The blood is pumped through the plate filter at a constant pressure of 500 mm Hg. The lost filtrate is continually replaced by Ringer lactate solution, which is added before the filter (Figure 3). Dogs were treated using a neck fistula, which allowed repeated punctures.

The following parameters were determined from the blood and filtrate samples: creatinine, amino acids (column chromatography), $^{14}$C–Inulin (Packard Liquid Scintillation Counter). From the blood specimens, free haemoglobin, fibrinogen, platelet and erythrocyte counts were estimated.
Ultrafiltration clearances were calculated according to the equation:

\[ \text{clearance} = \frac{\text{filtration flow} \times \text{filtration concentration}}{\text{whole blood concentration}} \]

and clearances for the dialyser determined by:

\[ \text{clearance} = \frac{\text{blood flow} \times (\text{concentration arterial} - \text{concentration venous})}{(\text{concentration arterial} - \text{concentration dialysate})} \]

Mean values together with their standard deviations were plotted. For the evaluation of significance, the Student’s t-test was used.

**RESULTS**

Figure 4 shows clearance data of creatinine, $^{14}$C–Inulin and $^{14}$C–EDTA for three different blood purification systems, namely plate filter, hollow fibre (filter) and the Gambro Lundia 18$\mu$ dialyser. In the plate filter all clearances are in the same range, independent of the molecular weight. In the hollow fibre, clearances of creatinine and EDTA are slightly lower, whereas the inulin clearance is markedly reduced. In the dialysis system, however, clearances of smaller molecules are very high, as expected, and the inulin clearance is extremely low. In the plate filter, the clearance values are mainly influenced by the filtrate flow, which is directly dependent on the filtration pressure and blood flow (Figure 5). In this system, increasing the blood flow rate over 100 ml/min has little effect on the filtrate volume. As Figure 6 shows, clearance values of different amino acids are in the range of 22–26 ml/min. The plasma concentration of the amino acids during the two hour filtration period was reduced in varying degrees, only being significant for arginine and histidine. During the filtration period, plasma fibrinogen decreased to 80% and platelets to 75% of the initial
Figure 4. Ultrafiltrate clearances of creatinine, $^{14}$C—EDTA and $^{14}$C—Inulin. (Hollow fibre Amicon HIDP 10.)

Figure 5. Relation between blood flow rate, filtration pressure and filtrate volume.
Figure 6. Clearances of amino acids and decreases of these substances during a two-hour ultrafiltration period.

Figure 7. Changes of fibrinogen levels, of haemolysis, and of platelet and erythrocyte counts during a two-hour ultrafiltration period.

values. Erythrocyte counts did not change, but haemolysis increased markedly (Figure 7).

**DISCUSSION**

Ultrafiltration clearance values are quite different from those obtained using dialysis systems. Related to the membrane surface, clearances of smaller molecules, e.g. creatinine are lower and clearances of larger molecules, e.g. inulin
higher. However, even for small molecules, ultrafiltration clearances exceeded peritoneal clearance values (Quellhorst, 1971). High serum levels of urea and creatinine do not result in clinical deterioration as Man (1973) showed in experiments with polyacryl-nitrate membranes. Inulin clearance values, which are higher than the clearances of vitamin B₁₂ obtained by Von Hartitzsch (1973) using Dow Cordis dialysers, indicate a sufficient elimination of ‘middle molecules’. A reduction of the time of treatment, without the clinical well-being of the patient being affected, may be possible. All clearances can be augmented by a higher ultrafiltrate flow, which can be achieved by increasing the filtrate pressure. This is, however, limited by damage to the blood cells. According to our own experience, pressure should not exceed 700 mm Hg.

Compared with dialyser membrane structure, the pore sizes in ultrafiltrate membranes are different, so that the loss of substances necessary for life must be carefully observed. Amino acid losses in our experiments were lower than those of Held (1974), who found a decrease of plasma levels to 66% during two hours of haemodialysis. Avivam (1971) registered amino acid clearances in haemodialysis experiments in the range of 49.5 ml/min and a total loss of 6–24 g. The minor elimination of amino acids by ultrafiltration may be explained by a reduced membrane transport of the fraction of bound amino acids in relation to dialysis, as observed by Kopple (1973) in haemodialysrer experiments.

Using an ultrafiltration system which results in high pressures (400–600 mm Hg) on blood cells, the question has to be answered whether haemolysis, well-known in uraemic patients, Blumberg (1972), is augmented to a dangerous level. In our ultrafiltration experiments, plasma haemoglobin levels were lower than values obtained with coil dialysers. However, they exceeded plasma haemoglobin levels which were found in Kil dialysers (Hyde, 1969). In haemolysis experiments, Indeglia (1968) registered significant increases of plasma haemoglobin after the augmentation of pressure to 6–10 psi. In spite of higher pressures in our experiments, haemolysis did not increase to such a degree. Lindsay (1973) observed a relation between the loss of fibrinogen and platelets during haemodialysis and the membrane thickness. Using cellulose nitrate membranes (thickness ~ 100μ), a serious hypofibrinogenenaemia was to be expected. However, a comparison of our results with those of Gerhartz (1964) and Köstering (1972) shows that the decrease of fibrinogen and platelets lies in the same range as was obtained by these authors for haemodialysis treatment.

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