MEMBRANES AND HAEMODIALYSIS

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Introduction

This manuscript resulted from a presentation we prepared jointly on the current and future status of membranes used to treat chronic uraemia. The manuscript covers the following points: (1) transport theory; (2) inadequacies in the evaluation of haemodialysers; (3) clinical trials with high flux dialysers used in the co-current mode; (4) some membranes that are needed and some that are not needed; (5) the importance of residual renal function in the clinical evaluation of new membranes.

Transport Theory

Migration phenomena of chemical species are traditionally, and arbitrarily, differentiated into (1) diffusive transport — the migration of the species resulting from its random thermal motion from a region of high chemical potential to a region of low chemical potential with molecular velocity restricted by molecular frictional interactions between the migrating species and all other chemical components of the system (2) convective transport — the migration of a volume element which frictionally interacts with an adjacent volume element. The transport coefficient used to depict convective transport is called 'viscosity' and the transport coefficient used to depict diffusion is called 'diffusivity'. These coefficients are often considered to be independent but in reality they are not, because of the fundamental dependence of each upon the same molecular interactions.

Frequently the combination solute + solvent is treated as a two component system. However, it should be noted that all such systems are in reality three component systems — solute, solvent and container, which may be a pipe or trough or capillary. If the container through which transport takes place is very small — several angstroms in diameter — it no longer acts as an inert part of the system and the molecular interactions between it and the solute and solvent
become strong. This is now a bona fide three component system with the container now called a 'membrane'. With the dimensions of the membrane pore size so small, the concepts of diffusivity and viscosity are of questionable validity and it becomes a practical necessity to describe transport phenomena without an in-depth molecular description of the process. Utilising a theory of 'non-equilibrium thermodynamics', it has been demonstrated that the transport coefficient matrix defined by this theory is symmetrical. As a consequence, it is possible to obtain a set of transport coefficients which is the minimal possible number necessary to characterise membrane transport phenomena. Staverman showed that, in addition to water and solute permeabilities, a third transport coefficient (the 'reflection coefficient') is necessary for complete characterisation of membrane transport [1,2].

**Haemodialysis/Haemofiltration**

When the transmembrane pressure is equal to the oncoitic pressure of the plasma, the volume flow across the membrane approaches zero, therefore the removal of solute results solely from a concentration difference or diffusivity, i.e., 'haemodialysis'. Thus in this situation, the rate of removal of any solute will depend primarily on maximising its concentration difference across the membrane and increasing its solute permeability. Practically, this is accomplished by running the dialysate flow countercurrent and also by making the pore size of the membrane as large as is practical. Haemofiltration is a technique where no dialysis occurs, solutes are simply carried across the membrane dissolved in a volume of ultrafiltrate; the membrane will select out solutes in accordance with the reflection coefficient.

It is standard procedure in most clinical settings to allow ultrafiltration and dialysis to proceed simultaneously. Using typical haemodialysis membranes, solutes of molecular weight less than about 150 daltons have their transfer governed primarily by diffusivity, the convective term having little importance. For substances with molecular weights above 150, transport by convection becomes increasingly more important. For removal of solutes around 1000 daltons, the ultrafiltration rate \((Q_u)\) amounts to \(30\% - 50\%\) of the transport of the solute. When the molecular weight increases above 3000 or 4000 daltons, only intensive ultrafiltration will remove significant amounts of these solutes.

**Characterisation of Haemodialysers**

Problems associated with correct characterisation of membrane transport phenomena are compounded when the membrane is packaged as a haemodialyser. These problems are easy to describe but difficult to correct and may be listed as:

1. There is a concentration gradient, not only across the membrane but also parallel to the membrane in the direction of the fluid flow, both on the blood side and on the dialysate side.
2. The channel geometry and membrane cannot be mass produced in a uniform manner. As a consequence, every type of dialyser as well as every individual dialyser will have somewhat different transport characteristics.

3. There is no possibility of rigorously evaluating all transport coefficients for a haemodialyser when ultrafiltration occurs; only semi-rigorous treatments involving no ultrafiltration across the dialyser are available [3].

The prevailing means for reporting clearance is the 'clearance versus blood flow diagram'. However, blood flow and transmembrane pressure are generally not resolved into independent experimental parameters; hence, clearance values at high blood flows are generally measured at different (and larger) ultrafiltration rates \(Q_v\) than clearances evaluated at low blood flows \(Q_v\) values are usually not listed). Therefore ultrafiltration increasingly influences values for clearance as the molecular size increases (middle molecules). For these reasons the traditional 'clearance versus blood flow diagram' introduces an intrinsic ambiguity into the data reporting process.

Because of this ambiguity, Zelman et al introduced an accurate and simple means of in vitro characterisation of dialysers. In brief, data from multiple in vitro experiments were fitted to the equations

\[
Q_v = AL_P \Delta P_m \quad (1)
\]

\[
C_i = \alpha_1 + \alpha_2 Q_v + \alpha_3 (Q_{Bi}) \quad (2)
\]

where \(\alpha_1, \alpha_2, \alpha_3\) are curve fitting parameters. The result was a very simple graphic format which is both easily read, accurate and unambiguous [4].

Clinical Research with High Flux Dialysers: Co-current Flow

The purpose of this research was to develop a simple and inexpensive haemodialysis protocol with the following objectives: 1) to utilise high flux dialysers in a single pass dialysis system with accurate control of ultrafiltration; 2) to maintain the transmembrane hydrostatic pressure, \(\Delta P_m\) at very small values; 3) to accomplish these first two objectives without the use of specialised equipment; 4) to characterise ultrafiltration as a function of \(\Delta P_m\) and time; 5) to characterise clearance as a function of ultrafiltration and time.

Mechanism for Ultrafiltration Control in Co-current Dialysis

Simplified, the mechanical force balance across the membrane anywhere inside the dialyser can be written as \(P_B = P_D + \nu\) where \(\nu\) is a restoring force supplied by the membrane. When the membrane is distensible, \(\nu\) tends towards zero and ultrafiltration tends toward a minimum value. In the co-current mode, the Transmembrane Pressure (TMP) across the dialyser is primarily due to the difference between \(P_{Bo}\) and \(P_{Do}\). A simple line clamp can be used to restrict the dialysate flow out of the dialyser, raising \(P_{Do}\) and lowering \((P_{Bo} - P_{Do})\) thus
regulating the pressure difference across the dialyser outlets. The membrane itself will automatically regulate the pressure across the dialyser inlets \((P_{Bi} - P_{Di})\) to a small value.

**Clinical Trials with the RP6 Used in the Co-current Mode**

In all experiments \(Q_B\) (225ml/min) and \(Q_D\) (500ml/min) were maintained constant.

*Ultrafiltration* Ten patients underwent single pass dialysis with the high flux RP6 dialyser used in the co-current mode. A valve on the dialysate outline enabled adjustment of \(\Delta P_m\) to be carried out rendering the dialysate pressure positive but less than \(P_{Bo}\). Ultrafiltration was easily controlled to a minimum value with simple dialysate valve adjustment. Two accurate pressure gauges, one on the blood outflow line and the other on the dialysate outflow line, allowed accurate measurement of TMP. The basic equation for \(Q_v\), using three coefficients can be written as follows:

\[
Q_v = \alpha_1 + \alpha_2 t + \alpha_3 \Delta P_m \quad t = \text{time in hours}
\]

In the clinical environment, using 30 sets of data obtained from the RP6 operated in the co-current mode, the ultrafiltration rate \((Q_v)\) is related to \(\Delta P_m\) and \(t\) as follows:

\[
Q_v = 12 \left( \Delta P_m - 8 - 6t \right) \text{ ml/hr/mmHg} \quad \text{(Figure 1)}
\]

*Clearance* Using the RP6 in the co-current mode, blood clearance values for creatinine, urea and phosphate were measured for three different ultrafiltration rates \((0, 1000\text{ml/hr}, 2000\text{ml/hr})\) with respect to time.

Using the basic equation \(C = \alpha_1 + \alpha_2 t + \alpha_3 Q_v\), the three coefficients \((\alpha_1, \alpha_2, \alpha_3)\) were calculated by multiple linear regression using five sets of data points. Results for \(C_{\text{creatinine}}\) are demonstrated in Figure 2 and may be expressed as:

\[
C_{\text{creatinine}} = 129 - 5.6t + 0.61 Q_v
\]

Similarly for clearances of urea and phosphate

\[
C_{\text{urea}} = 129 - 7t + Q_v \quad \text{and} \quad C_{\text{phosphate}} = 107 - 1.72t + 1.5Q_v
\]

It should be noted that both clearance and ultrafiltration decrease with time on dialysis using the RP6 dialyser. This is quite unambiguous and is probably due to protein deposition on the membrane.

**Which Membranes?**

*A research membrane with a cut-off at MW 500 daltons* In the early 70s, Babb and Scribner formulated what came to be known as the middle molecule hypo-
RP6 CO-CURRENT
ULTRAFILTRATION RATE $Q_V$ wrt TRANSMEMBRANE
PRESSURE $\Delta P_m$ and TIME $t$.

$$Q_V = 12(\Delta P_m - 8 - 6t) \frac{ml}{hr \cdot mmHg} \quad Q_{0B} = 225 ml/min$$
$$Q_V = 500 ml/min$$

$n = 30$
$r^2 = 0.95$

Figure 1

RP6 CO-CURRENT
BLOOD CREATININE CLEARANCE $C_{CRE}^B$ wrt TIME $t$
and ULTRAFILTRATION RATE $Q_V$.

$$C_{CRE}^B = 129 - 5.6 t \frac{ml}{min} \cdot 0.61 Q_V \frac{ml}{min} \quad Q_{0B} = 225 ml/min$$
$$Q_V = 500 ml/min$$

$n = 5$
$r^2 = 0.83$

AVERAGE DROP IN CLEARANCE: 5.6 ml/min-hr

Figure 2
thesis. To date, this hypothesis has been neither confirmed nor refuted. Despite this fact, a great deal of attention is currently paid to the removal of middle molecules, and membranes with high clearance for middle molecules are promoted actively. Clearly then, new attempts must be made to finally confirm or disprove the hypothesis that there are indeed toxic substances in the MW range 500 to 5000 daltons that must be removed to maintain the well-being of dialysis patients. Investigative efforts in this regard had the major flaw that whenever an attempt was made to manipulate middle molecules, parallel changes in the level of small molecules also occurred [5]. Therefore it became evident that what was needed to do these difficult experiments correctly was a new dialysis membrane with a sharp cut off at around 500 daltons. If such a membrane were available, it would be possible to repeat these experiments and attempt to induce pure middle molecule intoxication. Since these experiments are difficult and time-consuming, involving as much as two years of continuous study of each subject, it seems ill advised to repeat them until such a membrane becomes available.

Membranes to remove specific molecules From time to time, membrane chemists have complained that if nephrologists would tell them what uraemia toxin needed removal, they could fabricate the requisite membrane. There are two responses to this idea. First, it is folly to develop a membrane for removal of a specific uraemic toxin of the nitrogenous type. Since urea is toxic and uric acid is toxic and there are numerous other ‘uraemic toxins’, the syndrome of uraemia obviously is multifactorial. Secondly, if membrane chemists wish to fabricate a membrane that will selectively maximise the removal of a single compound, let them proceed with vigour to develop a membrane that selectively will remove phosphate.

Standard ultrafiltration: high middle molecule clearance Another task for the membrane chemists is to try and fabricate a membrane that has a very low diffusion resistance to middle molecules but a diffusion resistance to water at least as great as that of standard cuprophane membranes. If such a combination of characteristics were possible, we would have a very efficient dialyser with respect to both small and middle molecule clearance without having to cope with an obligatory high ultrafiltration rate.

Which Clinical Subjects?

Importance of residual renal function: the anuric patient Elsewhere in this volume will be published observations that support the idea that residual GFR in the range of 1–3ml/min provides up to 50% of the removal of middle molecules from patients on the usual dialysis regimens [6]. This observation makes it imperative that this variable be measured and controlled in any experiments dealing with middle molecule removal. For example, the only significant theoretical advantage of haemofiltration over diffusive dialysis is the greatly augmented removal of middle molecules. It is noteworthy that most of the patients who so far have been evaluated on haemofiltration are not anuric. Indeed, the majority seem to have residual GFR values > 1ml/min. In one study [7], the average residual GFR
of the nine subjects was 2.7ml/min. This level of GFR was nearly sufficient to remove middle molecules without any dialysis [8]. Hence it is doubtful whether a further increase in middle molecule removal, caused by the switch from haemodialysis to haemofiltration, would be detectable clinically. Obviously, a comparison using anuric subjects offers the best chance to demonstrate the beneficial effects of haemofiltration.

References

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Open Discussion

KERR (Newcastle) Dr Stephen did not speculate much on the mechanism of this fall off in clearance with time with high flux dialysers. Most of the explanations I can think of don't fit well with phosphate behaving differently from urea and creatinine. I would like to hear what you think is the mechanism.

STEPHEN First of all I should state that we are not too happy with these phosphate clearance values. There was quite a degree of error in them. I showed that slide because I think it demonstrates the way clearance falls with time. Now, we used two dialysers and we have the results complete for the RP6. For this dialyser I would say there is almost certainly packing of protein on the membrane. There was a nice, even linear fall off of clearance with time. On the other hand, with the Gambro high flux dialyser, the fall in clearance was an uneven jagged business. Now I spoke to the Gambro people here and they have used exactly the same dialyser frame for this high flux membrane, for the same area, and this membrane is some 22 micron thick as opposed to 11.5 micron in the ordinary Gambro major. In other words, there was tight packing. We used low heparin doses and when we took the membrane apart at the end of dialysis we found some clotting occurring in the different channels. So I think the mechanism for the two are quite different. One is probably protein packing on the membrane itself for the RP6, the other one probably blood clot in the dialyser.

KERR No evidence of air accumulation in the tightly packed dialyser?

STEPHEN No, we rather carefully avoided that.

FUNCK-BRENTANO (Paris) Would you agree, Dr Stephen, that besides the problem of protein packing there is, for phosphate, a problem of hydration of the molecule, so the real size across the membranes does not fit exactly with the
molecular weight.

STEPHEN Quite probably, I could not answer that properly, I am sorry.

FUNCK-BRENTANO Dr Scribner, I would like to support the concept you brought on Dialysis Index, which is about the same that we have proposed as the weekly clearance of Vit. B12. I think it must be seen as a practical tool. Everybody can agree with the definitions you gave because these are entirely arbitrary. You define adequate dialysis as a dialysis without any neuropathy, and middle molecule as a solute having a 1000 daltons molecular weight. This sounds reasonable and fits with what has been observed by those who are involved in middle molecule hypotheses. It is a useful tool to try to know what will be an adequate dialysis. This is the first point. This must not be mixed with the concept of middle molecules itself. There are a lot of peaks and a lot of groups working on these peaks.

SCRIBNER I agree completely with your ideas, the Dialysis Index simply is a substitute for a measurable middle molecule — just as creatinine is a marker for small molecules. How close do you think we are to having a marker molecule for some middle molecule, say a radio immunoassay for instance? If we had a radio immunoassay for a dialysable middle molecule then we could get rid of the dialysis index altogether. How close are we to that point?

FUNCK-BRENTANO We probably are very close to that. Peak b4—2 on which we are working contains a neurotoxic fraction which is not a polypeptide but a polyol. We know now the composition of this molecule so there is a good chance that we will soon measure the blood concentration of it on a wide scale. If the first results we have are confirmed, we will be able to measure the blood concentration of one specific middle molecule correlating with one uraemic sign, namely polyneuritis — then adequate dialysis, i.e. dialysis without polyneuritis, will be evaluated on a biochemical basis.

AHMAD (Liverpool) Professor Scribner, you showed in your slide that the vitamin B12 clearances do not show any appreciable change, beyond a dialysate flow rate of 150ml/min. We know from the published data, and a paper was presented at the ASAIO meeting in 1974 in Chicago showing no difference in clearances of small molecular weight substances with varying dialysate flow rates beyond 250ml/min. We have been using dialysate flow rates of 500ml/min for the past 15 years. Is it not time, to change and rationalise; thereby we would be saving an enormous amount of dialysate and energy?

SCRIBNER Let me answer first and then ask Dr Stephen as well. It is a perceptive question; I think Fred Shapiro in Minneapolis routinely dialyses now at QD250 or 200. One does sacrifice a little bit on urea clearance but as you correctly interpreted my slide, you influence almost not at all, clearance of higher molecular weight species. Bob, would you agree with that?

STEPHEN Yes, I will agree with that. We just maintain the dialysate flow rate constant at 500ml/min because that is a standard flow rate.

LEBER (Giessen) I just want to ask one question to this point. Professor Scribner,
you showed a slide demonstrating that the clearances of high molecular weight solutes is independent of the flow rates. In the KiiI dialyser this is true. But if you do investigations with a high flux membrane, i.e. with the RP6, you will find that even for molecules with a molecular weight up to 3,500 daltons there is an increase of the clearances with the dialysate flow rate.

SCRIBNER I don’t disagree. Let me clarify the point that my slide was based on relatively impermeable old style cuprophan. The reason that curve is flat is because the membrane has a relatively high resistance to the diffusion of middle molecules. The minute you get into a membrane that has higher permeability for middle molecules that diagram is no longer valid.

STEPHEN Just a general comment is that as we increase blood flow rates or dialysate flow rates, clearances increase, but they do asymptote more or less to a maximum. Just where that asymptote occurs depends on the permeability of the membrane. With the RP6, if I remember correctly, once one achieves blood flow rates of about 200 or 225ml/min increasing clearance is fairly minimal for a rather large increase in blood flow rate. Similarly, although I have not measured it, but I would suspect, clearance will increase very little for relatively large increases of dialysate flow rates when 300 or 400ml/min is exceeded.