Bi-directional Permeability of the Human Peritoneum to Middle Molecules

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Knowledge of the bi-directional permeability of the human peritoneum to various biochemicals and waste metabolites is essential for the characterisation of mass transfer occurring during peritoneal dialysis. The permeability characteristics of the peritoneum can only be inferred from the results of bi-directional solute mass transfer studies during peritoneal dialysis. These permeability characteristics are of major importance in the development of a suitable model for the evaluation of the effectiveness of peritoneal dialysis procedures. The present study was undertaken to (1) obtain bi-directional mass transfer data for solutes over a wide molecular weight range; (2) develop a suitable mathematical model from which solute peritoneal mass transfer coefficients can be computed, and (3) evaluate the results in light of the middle molecule hypothesis (MMH) (Babb et al, 1971).

This hypothesis has stimulated interest in the search for critical uraemic toxins (Ginn et al, 1971; Millora et al, 1972; Babb et al, 1972; Man et al, 1973; Chang & Migchelsen, 1973; Kopple et al, 1973). However, to date very little research has been done in determining peritoneal permeability characteristics for molecules larger than uric acid. Several researchers (Boen, 1964; Gross & McDonald, 1967; Wertheimer et al, 1967; Nolph et al, 1971) studied molecules of the size of uric acid and smaller but they all reported their findings in terms of peritoneal clearances rather than permeabilities. The clearance is not generally a good estimate of the permeability-area ($P_a A$) [Appendix] product particularly for small molecules such as urea.

Boen (1964), Henderson (1966), Henderson and Nolph (1969) and Aune (1970) have reported peritoneal clearance data. With the exception of Henderson and Nolph (1969) and Aune (1970) with their work on inulin, no peritoneal clearances for the middle molecule range of 300-5000 m. wt have been reported. However, a number of workers (Berlyne et al, 1964; Boen, 1964; Gordon & Rubini, 1967; Strauch et al, 1967) have studied the transfer of the plasma proteins across the peritoneum (approximately 90,000 m. wt). It is
well known that proteins do cross the peritoneum, and that protein loss may be a serious problem to patients undergoing peritoneal dialysis.

The effect of peritoneal dialysis operating conditions on clearances has been studied by a number of researchers (Boen, 1964; Shinaberger et al, 1965; Tenckhoff et al, 1965; Fernandez et al, 1966; Miller et al, 1966; Gross & McDonald, 1967; Lange & Treser, 1967; Penzotti & Mattocks, 1971). In general, these clearances depend on the dialysate flow rate. In this study, however, peritoneal mass transfer characteristics are compared in terms of $P_o A$ which is essentially independent of the peritoneal dialysis technique.

**EXPERIMENTAL PROCEDURE**

An in vivo experimental protocol was developed to determine the mass transfer characteristics of the human peritoneum during peritoneal dialysis with respect to solutes of different molecular weights. These solutes and their molecular weights are listed in Table I.

**Table I. Solutes used for peritoneal dialysis mass transfer studies**

<table>
<thead>
<tr>
<th>Solute</th>
<th>Molecular weight**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>60.1</td>
</tr>
<tr>
<td>Creatinine</td>
<td>113.1</td>
</tr>
<tr>
<td>Uric acid</td>
<td>168.1</td>
</tr>
<tr>
<td>$^{14}$C-Sucrose (1,670)</td>
<td>360</td>
</tr>
<tr>
<td>$^{57}$Co-Vitamin B$_{12}$ (1000)</td>
<td>1355</td>
</tr>
<tr>
<td>$^{14}$C-Inulin (3.4)</td>
<td>5200</td>
</tr>
<tr>
<td>$^{125}$I-RISA† (1.0)</td>
<td>68000</td>
</tr>
<tr>
<td>Plasma proteins</td>
<td>≈ 90000</td>
</tr>
</tbody>
</table>

* Original specific activity ($\mu$-curies/mg) of radioactive solutes is given in parenthesis

** Molecular weight of labelled molecule

† Radioactive-iodinated-serum-albumin (human)

The permeabilities of the endogenous substances in Table I (urea, creatinine, uric acid, and total proteins) were determined for efflux transfer only. Permeabilities of the exogenous, labelled solutes were determined for both efflux and influx experiments.

The rate of increase or decrease of a particular solute was determined. Urea, creatinine, and uric acid concentrations were measured by a Technicon Auto Analyzer. $^{14}$C-sucrose and $^{14}$C-inulin concentrations were determined by liquid scintillation; $^{57}$Co-vitamin B$_{12}$ and $^{125}$I-RISA concentration were analysed by a gamma counter.
The dialysate or blood concentration (as a function of time), the measured or assumed initial dialysate and blood distribution volumes, and the ultrafiltration rate, were then used with the proper mathematical formulation [Appendix] and computer program to determine the value of $P_0A$ for the solute studied.

The order in which the solutes were studied was established to allow for maximum accuracy. The first labelled solute studied was $^{14}\text{C}-\text{inulin}$ (influx). Its relatively slow diffusion into the body compartment caused only a small in vivo background radiation level which did not significantly interfere with the radiation count of the faster diffusing $^{14}\text{C}-\text{sucrose}$ (influx), the second labelled solute studied. Residual $^{14}\text{C}-\text{sucrose}$ body levels from the influx study would not interfere with the next study which was $^{14}\text{C}-\text{sucrose}$ efflux. The relatively high $^{14}\text{C}-\text{sucrose}$ level in the body after the $^{14}\text{C}-\text{sucrose}$ efflux study necessitated the use of the gamma-emitting $^{57}\text{Co}$-vitamin B$_{12}$ for the subsequent two studies of the first phase of the experiment. Beta emissions from the $^{14}\text{C}$ atoms did not interfere with the counting of $^{57}\text{Co}$-labelled substances.

The second phase of the study was begun only after the patient's body radiation levels were down to background levels (approximately one month after the end of the first phase). As in the first phase, the weak $\beta$-emitting $^{14}\text{C}-\text{inulin}$ (efflux) was run first so it would not be affected by the $\gamma$-emitting $^{125}\text{I}$-RISA. To check if the peritoneal membrane had markedly changed during the time between part 1 and part 2, the permeabilities of endogenous compounds were determined again.

**PATIENT SELECTION**

The patients chosen for this study were adult uraemics who were free of peritonitis and had been undergoing peritoneal dialysis for at least one month. All patients had permanently implanted silastic peritoneal catheters which assured unrestricted dialysate inflow and drainage. Since all the subjects studied had either undergone nephrectomies or had negligible urinary output, the effect of residual renal function was not a factor.

**EFFLUX MEASUREMENTS**

For exogenous solute efflux studies the patient was given, intravenously, a precisely measured dose of the labelled compound to be studied. About 90 minutes were allowed for distribution of the solute throughout the body fluids, during which time several blood samples were taken. These samples were later counted and used for body-volume determinations (Guyton, 1971). During the above period the peritoneal cavity remained empty.

Next several wash-out cycles for both exogenous and endogenous solutes were performed, then approximately 1500ml of dialysate were infused into
the peritoneal cavity. * The zero-time samples of the patient’s blood and the
dialysate were obtained approximately five minutes later. Additional blood
and dialysate samples were taken at pre-determined times over the estimated
60 minute period the dialysate remained in the cavity. At the end of this
period the dialysate was drained into a 2 litre bottle and a final dialysate
sample was taken from this bottle. Since this last sample was well mixed it
served as a check on the dialysate sample taken from the cavity.

INFLUX MEASUREMENTS

For solute influx studies (exogenous compounds only), the labelled compound
to be studied was added to the infusing dialysate. Addition of the labelled sol-
ute was complete after approximately 2/3 of the dialysate had infused into
the cavity. After a five-minute equilibration period, the zero-time blood and
dialysate samples were taken; the remainder of the study was identical to the
efflux procedure.

ULTRAFILTRATION

In order to determine ultrafiltration rates, inflow and outflow dialysate vol-
umes were measured. The inflow volume was determined by letting approxi-
aturally 1500ml drain from the overhead gravity feed bottle. The outflow vol-
ume was determined by draining the spent dialysate from the patient directly
into a 2000ml bottle and then measuring its volume. The ultrafiltration rate
was calculated from:

\[ Q_u = \frac{\text{outflow volume} + \text{sample volume} - \text{inflow volume}}{\text{cycle time}} \]  \hspace{1cm} (1)

The sample volume is the total number of samples taken during the experi-
ment multiplied by the volume of each sample, and the cycle time is abituar-
ly defined as the dwell time plus one-half the sum of the inflow and outflow
times. The recovery of the infused volume and ultrafiltrate is aided by an
indwelling silastic catheter which was implanted at least four weeks prior to
the study.

CLEARANCES

For the sake of completeness, clearances were calculated for all the efflux
studies. These clearance values were calculated using the following mathem-
aatical relationship between peritoneal clearance and \( P_o A \) which was derived
(Johansen, 1973) for the efflux case with zero ultrafiltration and a constant
rate of inflow and outflow:

*A wash-out cycle consisted of introducing about 1500ml of dialysate into
the peritoneal cavity, letting it remain there for no more than five minutes,
and then draining it.
\[ K_P = P_0 A \left[ 1 - \frac{P_0 A t}{2V_D} + \frac{1}{6} \left( \frac{P_0 A t}{V_D} \right)^2 \ldots \right] \] (2)

where \( K_P \) = clearance
\( V_D \) = total accumulated dialysate volume at the end of dialysis
\( t \) = overall time on dialysis (the sum of all inflow, dwell and outflow times)

It is evident from equation (2) that the clearance is only equal to \( P_0 A \) for short dwell times and/or small values of \( P_0 A \) which are characteristic of large molecules. This implies that great care should be used when comparing different dialysis techniques using the clearance concept rather than \( P_0 A \).

RESULTS

Peritoneal mass transfer studies were conducted on three 'normal' anuric uraemic patients undergoing peritoneal dialysis. The \( P_0 A \) values computed from equation (14) for the three patients studied are presented in Tables II to V. As can be seen from these tables, a complete two-part study was accomplished only on patient LV. Studies on the other patients had to be terminated prematurely for a variety of reasons such as a renal transplant.

The results presented in Tables II-V are subject to error due to a number of variables that were difficult to measure and control during the experiments.

The most important variable, affecting the accuracy of the results was the effect of ultrafiltration on the mass transfer rate. First, it was not possible to measure this variable accurately, and, second, the individual solvent

<table>
<thead>
<tr>
<th>Table II. Peritoneal dialysis ( P_0 A ) values for patient EM*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solute</strong></td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Urea</td>
</tr>
<tr>
<td>Creatinine</td>
</tr>
<tr>
<td>Uric acid</td>
</tr>
<tr>
<td>( ^{14} )C-Sucrose</td>
</tr>
<tr>
<td>( ^{57} )Co-Vitamin B( _{12} )</td>
</tr>
<tr>
<td>( ^{14} )C-Inulin</td>
</tr>
<tr>
<td>Proteins</td>
</tr>
</tbody>
</table>

*Age: 51 years; weight: 47kg; height: 157cm; sex: female; haematocrit: 21.0%; Qu = 39 ± 0.80ml/min; anephric

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Table III. Peritoneal dialysis $P_oA$ values for patient AH*

<table>
<thead>
<tr>
<th>Solute</th>
<th>Efflux $Tr = 0.0$</th>
<th>Efflux $Tr = 1.0$</th>
<th>Influx $Tr = 0.0$</th>
<th>Influx $Tr = 1.0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>18.0 ± 1.33</td>
<td>15.2 ± 0.88</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Creatinine</td>
<td>7.03± 0.51</td>
<td>4.88± 1.16</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Uric acid</td>
<td>5.52± 0.39</td>
<td>3.47± 1.20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$^{14}$C-Sucrose</td>
<td>-</td>
<td>-</td>
<td>2.33 ± 1.23</td>
<td>2.36 ± 1.21</td>
</tr>
<tr>
<td>$^{14}$C-Inulin</td>
<td>-</td>
<td>-</td>
<td>1.45 ± 1.28</td>
<td>1.46 ± 1.27</td>
</tr>
<tr>
<td>Proteins</td>
<td>0.11± 0.01</td>
<td>-1.63± 1.35</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Age: 21 years; weight: 69kg; height: 189.6cm; Sex: male- haematocrit: 15.5%; $Qu = 1.7 ± 1.3$ml/min; anephric

Table IV. Peritoneal dialysis $P_oA$ values for patient LV (run 1)*

<table>
<thead>
<tr>
<th>Solute</th>
<th>Efflux $Tr = 0.0$</th>
<th>Efflux $Tr = 1.0$</th>
<th>Influx $Tr = 0.0$</th>
<th>Influx $Tr = 1.0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>23.8 ± 1.83</td>
<td>20.3 ± 0.64</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Creatinine</td>
<td>10.9± 0.72</td>
<td>8.50± 0.99</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Uric acid</td>
<td>10.4 ± 0.73</td>
<td>8.00± 1.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$^{14}$C-Sucrose</td>
<td>6.49± 0.44</td>
<td>4.27± 1.14</td>
<td>6.74 ± 1.07</td>
<td>6.51 ± 1.05</td>
</tr>
<tr>
<td>$^{57}$C-Vitamin B$_{12}$</td>
<td>5.38± 0.37</td>
<td>2.31± 1.19</td>
<td>4.22 ± 1.13</td>
<td>4.23 ± 1.11</td>
</tr>
<tr>
<td>$^{14}$C-Inulin</td>
<td>-</td>
<td>-</td>
<td>2.74 ± 1.19</td>
<td>2.76 ± 1.17</td>
</tr>
<tr>
<td>Proteins</td>
<td>0.21± 0.02</td>
<td>-1.62± 1.30</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Age: 38 years; weight: 64.5kg; height: 160.8cm; sex: female; haematocrit: 23.5%; $Qu = 1.8 ± 1.3$ml/min; anephric

Table V. Peritoneal dialysis $P_oA$ values for patient LV (Run 2)*

<table>
<thead>
<tr>
<th>Solute</th>
<th>Efflux $P_oA$ (ml/min) $Tr = 0.0$</th>
<th>Efflux $P_oA$ (ml/min) $Tr = 1.0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>20.0 ± 1.26</td>
<td>15.9 ± 0.61</td>
</tr>
<tr>
<td>Creatinine</td>
<td>12.2 ± 0.71</td>
<td>8.94 ± 0.76</td>
</tr>
<tr>
<td>Uric acid</td>
<td>9.66 ± 0.56</td>
<td>6.62 ± 0.81</td>
</tr>
<tr>
<td>$^{14}$C-Inulin</td>
<td>4.70 ± 0.28</td>
<td>2.07 ± 0.91</td>
</tr>
<tr>
<td>Proteins</td>
<td>0.18 ± 0.02</td>
<td>-2.08 ± 0.99</td>
</tr>
</tbody>
</table>

*Qu = 2.2 ± 1.0ml/min

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drag coefficients (Tr) are unknown for the peritoneum. Hence calculations were completed for the two extremes Tr = 1 and Tr = 0.

It is interesting to note the effect of inaccuracies in Q_u on P_oA for different-sized molecules and different values of Tr. If Tr = 0, the incoming ultrafiltrate does not carry any solute, and the only effect of ultrafiltration is to dilute the dialysate. This decreases the solute dialysate concentration and enhances diffusive efflux. For this case the error associated with Q_u is fairly constant for all values of P_oA and decreases in absolute value as the molecular size increases. If Tr = 1, however, the solute is carried into the peritoneal cavity with the ultrafiltrate at the plasma-concentration. For small molecules, such as urea, the diffusive transfer is so large that convection is only a minor mode of transfer, and the P_oA variance is relatively small. Large molecules, on the other hand, such as inulin, diffuse relatively slowly, and if Tr = 1, the contribution of convection to solute transfer can be very significant. For this reason errors in measuring Q_u can seriously affect the accuracy of large-molecular P_oA values. Looking at the data for patient LV, with a Q_u of 1.8ml/min ± 70%, the urea P_oA is 20.3ml/min ± 3% while the inulin P_oA is 2.3ml/min ± 50%.

It should be emphasized that P_oA is theoretically constant. When calculated using the correct value of Tr, P_oA should be the same for any ultrafiltration rate. Biological membranes, however, are alive and as such are capable of changing their properties. It is entirely possible that high rates of ultrafiltration could irritate the peritoneum, causing changes in the pore size and therefore in P_oA. In actuality, therefore, P_oA could be a function of Q_u.

MIDDLE MOLECULE REMOVAL

The middle-molecule mass-transfer properties of the peritoneum can be best understood by plotting solute P_oA values versus molecular weight as in Figure 1 for patient LV (Efflux data with Tr = 0). For comparison h_oA* values for standard Kiil and Model 3 Dow HFAK haemodialysers are also plotted.

As expected, P_oA values for the peritoneal dialysis are significantly lower than the corresponding h_oA values for the two haemodialysers in the lower molecular weight range. However, for molecular weights above 1000 P_oA values decrease only slightly compared to the significant decrease in the h_oA values for haemodialysers. In addition, the h_oA m.wt curve for the Model 3 Dow HFAK crosses that for the peritoneal dialysis at a molecular weight of about 3000 and is about a factor of two lower at a molecular weight corresponding to inulin. The standard Kiil dialyser h_oA curve on the other hand does not cross the peritoneal P_oA curve until the molecular weight of

\*h_o is the overall solute mass transfer coefficient for haemodialysis
Figure 1. Variation of $P_0A$ and $h_0A$ with solute molecular volume

inulin is reached. Based on these data, one would expect that pre-dialysis concentrations of solutes below a molecular weight of 3000–5000 would be significantly higher for peritoneal dialysis protocols compared to standard haemodialysis protocols. However, above a molecular weight of 5000 the peritoneal dialysis protocol should give lower pre-dialysis concentrations than even a standard Kiil dialysis protocol (3.8 = 24 hr/week, of dialysis at $Q_D = 500$ ml/min, $Q_B = 200$ ml/min, $Q_u = 0$ and $K_K = 0$) [Appendix].

One way of comparing the expected chemical effect of a given peritoneal dialysis protocol on a patient relative to that expected for standard haemo-

<table>
<thead>
<tr>
<th>Solute</th>
<th>Tr = 0.0 LV Run 1</th>
<th>Tr = 0.0 LV Run 2</th>
<th>Tr = 0.0 EM</th>
<th>Tr = 1.0 LV Run 1</th>
<th>Tr = 1.0 LV Run 2</th>
<th>Tr = 1.0 EM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.46</td>
<td>0.61</td>
<td>0.55</td>
<td>0.42</td>
<td>0.56</td>
<td>0.48</td>
</tr>
<tr>
<td>Uric acid</td>
<td>0.44</td>
<td>0.48</td>
<td>0.49</td>
<td>0.39</td>
<td>0.42</td>
<td>0.41</td>
</tr>
<tr>
<td>Sucrose</td>
<td>0.27</td>
<td>-</td>
<td>0.40</td>
<td>0.21</td>
<td>-</td>
<td>0.32</td>
</tr>
<tr>
<td>Vitamin B$_{12}$</td>
<td>0.23</td>
<td>-</td>
<td>0.32</td>
<td>0.11</td>
<td>-</td>
<td>0.20</td>
</tr>
<tr>
<td>Inulin</td>
<td>-</td>
<td>0.23</td>
<td>-</td>
<td>0.13</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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Table VII. Peritoneal solute-to-urea $P_oA$ values compared to haemodialyser $h_oA$ values

<table>
<thead>
<tr>
<th>Solute</th>
<th>Peritoneal patient LV</th>
<th>Standard Kiil</th>
<th>Model 3 Dow HFAK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (60.1)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Creatinine (113.1)</td>
<td>0.60</td>
<td>0.65</td>
<td>0.54</td>
</tr>
<tr>
<td>Uric acid (168.1)</td>
<td>0.47</td>
<td>0.50</td>
<td>0.37</td>
</tr>
<tr>
<td>Sucrose (360)</td>
<td>0.35</td>
<td>0.31</td>
<td>0.19</td>
</tr>
<tr>
<td>(800)*</td>
<td>0.29</td>
<td>0.18</td>
<td>0.08</td>
</tr>
<tr>
<td>Vitamin B12 (1355)</td>
<td>0.26</td>
<td>0.13</td>
<td>0.05</td>
</tr>
<tr>
<td>(2500)*</td>
<td>0.23</td>
<td>0.07</td>
<td>0.022</td>
</tr>
<tr>
<td>Inulin (5200)</td>
<td>0.21</td>
<td>0.03</td>
<td>0.008</td>
</tr>
<tr>
<td>(10,000)**</td>
<td>0.19</td>
<td>0.02</td>
<td>0.003</td>
</tr>
<tr>
<td>(20,000)**</td>
<td>0.17</td>
<td>0.01</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* interpolated data from Figure 1
** extrapolated data from Figure 1 (Farrell et al, 1973)

dialysis protocols is to compute the $P_oA$ and $h_oA$ values for each solute relative to urea as shown in Tables VI and VII. It is evident that for equivalent urea removal, a patient undergoing peritoneal dialysis would have to spend more time on dialysis than a patient on haemodialysis. Furthermore, equivalent urea removal would result in somewhat lower peritoneal dialysis removal of creatinine and uric acid, about the same removal for molecules with molecular weights about that of sucrose and significantly greater removal of solutes above a molecular weight of 3000.

DISCUSSION

The middle molecule hypothesis (MMH) grew out of the observation (Scribner, 1965) that patients on peritoneal dialysis remained free of neuropathy despite seemingly inadequate dialysis. This was attributed to the speculation that higher molecular weight solutes were more effectively removed during peritoneal dialysis than during standard haemodialyses. The results of this present study confirm the speculation based on the relative values of the solute-to-urea $P_oA$ and $h_oA$ values and to this extent support the MMH.

Patients on peritoneal dialysis may have the best overall type of molecule removal, namely, adequate removal of middle molecules without excessive removal of small molecules. This speculation demands further investigation of the whole question of the effects of either excessive or inadequate removal of substances of various molecular weight on patient well-being. The results of this investigation are likely to complicate further the problem of providing truly optimal dialysis since decreasing the removal of
one type of small molecule to correct a deficiency may cause interaction due to retention of other molecules in the same molecular weight range.

CONCLUSIONS

1 During peritoneal dialysis lower molecular weight solutes are removed at much lower rates than in standard haemodialysis.

2 Higher molecular weight solutes are removed at significantly higher rates relative to urea than in haemodialysis.

3 The longer peritoneal dialysis times are primarily to reduce the concentrations of lower molecular weight solutes to acceptable levels rather than those of higher molecular weights.

4 Despite the fact that small molecule peritoneal clearances are 1/4 to 1/6 of those in haemodialysers, peritoneal patients maintain their well-being. This is consistent with our idea that standard haemodialysis may produce deficiencies.

5 The absence of neuropathy and other evidence of toxicity in peritoneal patients may be attributable to the greater removal of middle molecules.

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REFERENCES

APPENDIX
MATHEMATICAL MODEL FOR THE DETERMINATION OF P_{OA}

Nomenclature

**Symbols**

A  
Effective area of peritoneum

C  
Concentration

m,M  
Mass of solute

P_o  
Overall peritoneal mass transfer coefficient

Q  
Volumetric flow rate

t,T  
time

Tr  
'Transmittance coefficient' of solvent drag coefficient

u  
Ultrafiltration velocity

V_B  
Single pool volume

V_D  
Dialysate volume

K_K  
Renal creatinine clearance

**Subscripts**

B  
Blood phase

C  
Convective

D  
Dialysate

d  
Diffusive
The following model of mass transfer during the dwell period of a peritoneal dialysis cycle was developed by Johansen (1973) and is based on passive solute transport both by convection and diffusion across the peritoneal membrane. The peritoneum is defined to be all of the membranous material separating the capillary blood from the dialysate fluid, specifically the visceral and parietal membranes.

If one assumes that the diffusive transport into the peritoneal cavity can be described by Fick's law, then, at steady-state, the rate of solute mass entering the cavity by diffusion, \( \frac{dM_d}{dt} \), can be written:

\[
\frac{dM_d}{dt} = \int P_o \ (C_{B_1} - C_D) \ dA
\]  

(3)

where \( P_o \) is the overall mass transfer coefficient*, \( C_B \) and \( C_D \) are the blood and dialysate concentrations of the well mixed body fluid and dialysate distribution volumes (\( V_B \) and \( V_D \), respectively), and \( dA \) is the differential effective transport area of the peritoneum. The subscript one refers to the end of the inflow period. If \( P_o \), \( C_{B_1} \) and \( C_D \) are independent of the peritoneal effective area then equation (3) becomes:

\[
\frac{dm_d}{dt} = P_o A \ (C_{B_1} - C_D)
\]  

(4)

The rate of solute mass transport to the peritoneal cavity as a result of convection, \( \frac{dm_c}{dt} \), can be written as:

\[
\frac{dm_c}{dt} = \int Tr \ C_B \ u \ dA
\]  

(5)

where \( Tr \) is a 'transmittance coefficient' which reflects the interaction between the solute molecular properties and the membrane pore characteristics and can range between zero and one, and \( u \) is the ultrafiltration velocity. If \( Tr \), \( C_B \), and \( u \) are independent of membrane area, equation (5) becomes:

\[
\frac{dm_c}{dt} = Tr \ C_B \ Q_u
\]  

(6)

where \( Q_u \) is the rate of ultrafiltration.

The total rate of change of mass of a dialysate solute in the peritoneal cavity is a linear combination of mass transfer rates due to both convection and diffusion, and equations (4) and (6) can be combined to give:

\[
\frac{dm}{dt} = P_o A \ (C_{B_1} - C_D) + Tr \ C_B \ Q_u
\]  

(7)

*\( P_o \) is inversely proportional to the sum of the blood-side film, the peritoneum, and the dialysate-side film resistance to diffusion.
From a dialysate side material balance \( \frac{d}{dt} \) can also be written as:

\[
\frac{dm}{dt} = \frac{d(C_D V_D)}{dt} = V_D \frac{dC_D}{dt} + C_D \frac{dV_D}{dt}
\]  
(8)

where \( V_D \) is the dialysate volume at any time, \( t \). If the ultrafiltration rate, \( Q_u \), is assumed to be constant then:

\[
V_D = V_{D1} + Q_u t
\]  
(9)

where \( V_{D1} \) is the dialysate volume at the beginning of the diffusion period. The rate of increase in \( V_D \) is due to bulk flow so that

\[
\frac{dV_D}{dt} = Q_u
\]  
(10)

Since the sum of the masses of a particular solute in the body compartment and the peritoneal cavity is constant, a material balance yields:

\[
C_{B1} V_{B1} + C_{D1} V_{D1} = M_1 = C_B V_B + C_D V_D
\]  
(11)

where the subscript one refers to values at the end of the inflow period. \( M_1 \) is the total initial solute mass in the body and dialysate compartments. From a volume balance:

\[
V_B = V_{B1} - Q_u t
\]  
(12)

Substituting equations (8) through (12) into equation (7), the general differential equation representing the change in the dialysate concentration with time is obtained:

\[
\frac{dC_D}{dt} + \left( \frac{P_A + Q_u}{V_{B1} - Q_u t} + \frac{P_A + Q_u}{V_{D1} + Q_u t} \right) C_D = \frac{(P_A + Q_u) Tr}{(V_{B1} - Q_u t) (V_{D1} + Q_u t)} M_1
\]  
(13)

Computer Solution for \( P_A \)

Equation (13) can be rearranged so that \( P_A \) stands alone:

\[
P_A = \frac{V_B V_D (dC_D/dt) + Q_u [C_D (V_B + Tr V_D) - Tr M_1]}{M_1 - C_D (V_B + V_D)}
\]  
(14)

where \( V_B = V_{B1} - Q_u t \), and \( V_D = V_{D1} + Q_u t \). This equation is valid for both efflux and influx mass transfer when ultrafiltration is occurring into the peritoneal cavity and lends itself quite readily to computer solution. The following is the solution technique employed:

1. Obtain \( C_D \) vs. \( t \) data for particular solute from in vivo experiments.

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From these data, the equation for the line of best fit (using a least-mean-squares technique) is determined.

From this equation, \( C_D \) and \( dC_D/dt \) at any given time are obtained.

Since \( C_{B1} \), \( V_{B1} \), \( V_{D1} \), \( Q_u \), and \( Tr \) are known, equation (14) can be solved for \( P_0 A \).

OPEN DISCUSSION

R PAPOVICH (University of Texas): How long did you leave the fluid in the cavity? And did you vary the time that the fluid was in the cavity to show that indeed \( P_0 A \) is independent of this time. The reason I ask is that we have some preliminary data that shows that indeed it might be dependent upon time.

BABBB: Over the range we studied the \( P_0 A \) was essentially constant, but this may not be true over a wider range.

V CAMBI (Parma): It is true that peritoneal dialysis patients can do well, but there is no difference with regard to neuropathy between haemodialysis and patients on peritoneal dialysis. You show now that the difference in middle molecule removal is enormous. We should expect that if middle molecules are specifically toxic, that the patient on peritoneal dialysis should be better than the patient on haemodialysis.

BABBB: I defer the question to my medical colleague, Dr Tenckhoff.

TENCKHOFF: Patients do as well, but certainly not better than haemodialysed patients. Actually, we don't know what kind of middle molecules we are talking about. There may be relatively small molecules in the middle molecule range, which are more efficiently removed by haemodialysis than peritoneal dialysis. There is no definite answer.

T BUSELMEIER (Minneapolis): Can you use neuropathy, anaemia, and pericarditis as measures of the adequacy of dialysis? Anaemia may be related to phosphorus, acidosis, and other things, and pericarditis is sometimes not cured with adequate dialysis. Why implicate middle molecules when other factors are known to be important?

BABBB: My comment there will be rather short. You are certainly correct in that we ought to recognise when we talk about the well-being of a patient
it is a very subjective judgment. But on the other hand I would like to point out to you that the patients on whom we carry out these research studies are stabilised. They are not in a transient unsteady state where it is difficult to delineate what factors are changing and causing the important effects.