Influence of Convection on the Diffusive Transport and Sieving of Water and Small Solutes across the Peritoneal Membrane

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The three-pore model of peritoneal membrane physiology predicts sieving of small solutes as a result of the presence of a water-exclusive pathway. The purpose of this study was to measure the diffusive and convective components of small solute transport, including water, under differing convection. Triplicate studies were performed in eight stable individuals using 2-L exchanges of bicarbonate buffered 1.36 or 3.86% glucose and icodextrin. Diffusion of water was estimated by establishing an artificial gradient of deuterated water (HDO) between blood/body water and the dialysate. 125I-RISA (radio-iodinated serum albumin) was used as an intraperitoneal volume marker to determine the net ultrafiltration and reabsorption of fluid. The mass transfer area coefficient (MTAC) for HDO and solutes was estimated using the Garred and Waniewski equations. The MTAC of HDO calculated for 1.36% glucose and icodextrin were similar (36.8 versus 39.7 ml/min; P = 0.3), whereas for other solutes, values obtained using icodextrin were consistently higher (P < 0.05). A significant increase in the MTAC of HDO was demonstrated with an increase in the convective flow of water when using 3.86% glucose (mean value, 49.5 ml/min; P < 0.05). MTAC for urea was also increased with 3.86% glucose. The identical MTAC for water using 1.36% glucose and icodextrin indicates that diffusion is predominantly through small pores, whereas the difference in MTAC for the remaining solutes is a reflection of their sieving. The increase in the MTAC of water and urea associated with an increase in convection is most likely due to increased mixing within the interstitium.


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sieving. We anticipated that by combining the measurements of intraperitoneal volume with the creation of an artificial deuterated water (HDO) gradient, it would be possible to dissect the diffusive versus convective transport of water across the membrane. In addition, by allowing comparison of diffusive transport between small solutes, under conditions of iso-osmotic versus hypertonic dialysis, it should be possible to demonstrate the process of sieving for small solutes, e.g., urea and creatinine, but not for water.

Materials and Methods

Study Design
The mechanisms of peritoneal water transport were explored by combining intraperitoneal volume measurements (13) to determine the net ultrafiltration and reabsorption, with an artificially created deuterated water gradient (HDO), to determine diffusion (14). The different pathways of water transport were investigated by creating conditions of low and high convection through both pore systems (using 1.36 and 3.86% glucose, respectively) and by confining convective flow to the intercellular pores using icodextrin.

Eight stable patients who were established on peritoneal dialysis and had no recent episodes of peritonitis were recruited. To minimize impact of patient variability, e.g., sump volumes, peritoneal surface area, and osmotic hydraulic conductance, we performed triplicate studies in each individual using both glucose concentrations (1.36 and 3.86%) and icodextrin. Informed patient consent and approval from the local ethics committee were obtained.

Experimental Protocol

Our method combining the use of an intraperitoneal volume marker (13) with the generation of an HDO concentration gradient was described recently in detail (14). Briefly, the patient consumes a small volume of pure (99.9%) deuterium oxide (dose of 0.3 g/kg), and his deuterium abundance within the dialysate samples was determined by a combination of enzymatic assay methods with the use of an automated discrete random access analyser (DAX 72; Bayer Instruments, Basingstoke, UK); sodium was measured with the same equipment using the indirect ion electrode method, which for dialysate gives equivalent results to flame photometry in our laboratory. Plasma sodium was corrected for the Gibbs-Donnan effect, correction factor 0.96. The dialysate creatinine levels were corrected for the effect of the high dialysate glucose concentration. Radioactivity was determined from triplicate samples using an Intertechnique gamma counter. The background radiation was accounted for, and the percentage error between each sample was within the order of 1 to 1.5%. Consistent reproducibility was demonstrated in our tracer technique with the recovery of isotope on completion of the peritoneal exchange averaging at 86.3% (SD ±7.2) (13,19) calibrated against a prepared standard for each individual experiment.

Calculation of Intraperitoneal Volume Profiles
The mathematical principles developed by Lindholm et al. (13) were used to determine the apparent (Va(t)) and actual (Vd(t)) intraperitoneal volumes during the course of the peritoneal exchange. The calculation of Va(t) (equation 1) assumes no loss of isotope from the peritoneal cavity and therefore will overestimate the peritoneal volume; this volume can be determined by measuring the radioactivity within the dialysate sample at any time point, Ct(t), the initial instilled dialysate volume, V0, and the initial radioactivity count, C0. Significant volumes of fluid are drawn during the course of the peritoneal exchange for purposes of analysis, and these were accounted for within the calculations (13):

\[ V_{a(t)} \cdot C(t) = V_0 \cdot C_0 \] (1)

The calculation of the actual peritoneal volume, Vd(t) (Eq. 2), uses first-order kinetics for the disappearance of the tracer molecule from the peritoneal cavity:

\[ V_{d(t)} = V_{a(t)} \left( 1 - \frac{V_{a(t)} - (V_{out} + V_{res}) t}{V_a(T)} \right) \] (2)

where, \( V_{res} \) is the residual volume (estimated from the “rinse exchange” after the “test exchange”), \( V_T \) and \( V_{res} \) represent the final apparent volume and the final drained volume, respectively, and \( T \) is the duration of the “test exchange.”

The net ultrafiltration of fluid was determined by subtracting the initial instilled fluid volume at the start of the peritoneal exchange from the calculated Vd; for purposes of standardization and to allow comparison of data, these values were normalized to a value of 2 L. The differences between the two calculated volumes, Va(t) and Vd(t), during the course of the exchange exhibited a linear relationship, and the calculated gradient of this slope represented the reabsorption of fluid (L).

The best-fit exponential relationship as described by Rippe et al. (20,21) (Eq. 3) was used to describe individual volume profiles with greater precision. The best-fit volume at any time point, Vt, follows an exponential relationship, where V0 defines the initial instilled peritoneal volume, whereas \( a_1, a_2, k \) are coefficients defining this relationship. As repeat studies were conducted in each individual, it was possible to use the paired glucose data to determine a common value for \( a_2 \) for each individual, which then was incorporated into the unweighted least squares method to determine the best-fit volume profiles. For the icodextrin dwell, ultrafiltration could be described as a linear function (19).

\[ V_t = V_0 + a_1(1 - e^{-kt}) - a_2t \] (3)
Calculation of MTAC

The simplified Garred equation (see Eq. 4) was used to calculate the MTAC for solutes and HDO (10). For solutes, we used the intraperitoneal volume (best-fit calculated volume, Vt) and dialysate (Dt) solute measurements at 120 min, as diffusive transport is maximal during this phase of the exchange, whereas for HDO, an average of our data at 30 to 60 min was used, as we have previously demonstrated that the time constants for deuterium/water range from 33 to 53 min. Asymptotic or equilibrated values for dialysate deuterium abundance are representative of the plasma values and were used in the calculation of the MTAC of water:

\[
\text{MTAC} = \frac{V_t}{t} \ln \frac{V_0(P - D_0)}{V_t(P - D_t)}
\]

We also used the Waniewski equation (see Eq. 5) (10) to determine MTAC, which attempts to correct further for convective flow, F, depending on the degree of ultrafiltration (where \( F = 0.33 \) or 0.5, for high or low levels of ultrafiltration, respectively); this method also uses the mean intraperitoneal volume (Vm) for the calculation of the MTAC:

\[
\text{MTAC} = \frac{V_m}{t} \ln \frac{V_0^{1-F}(P - D_0)}{V_t^{1-F}(P - D_t)}
\]

Statistical Analyses

The paired, two-tailed ANOVA \( t \) test was used for data comparison among the three different dialysate fluids. \( P < 0.05 \) was considered to be statistically significant.

Results

Patient Demographics

Eight stable male peritoneal dialysis patients were studied; their mean age was 55 yr, and the average time on peritoneal dialysis therapy was 21 mo. Solute transport status ranged from 0.542 to 0.801 as determined by the dialysate to plasma creatinine at 4 h (Table 1).

Volume Curves and Evidence of Sodium Sieving

Ultrafiltration and fluid reabsorption profiles for each of the three different dialysate fluids are depicted in Figure 1. The mean (±SD) initial ultrafiltration rates, as calculated from the differential continuity equation (19), were 0.79 (±3), 8.68 (±2.5), and −0.5 (±12.1) ml/min for 1.36 and 3.86% glucose and icodextrin, respectively. No statistically significant differences were found between the reabsorption of fluid for the three different dialysate fluids (mean reabsorption rates, 0.64, 0.55, and 0.74 ml/min for 1.36 and 3.86% glucose and icodextrin, respectively).

The dialysate/plasma (D/P) sodium profiles are shown (Figure 1b) for each of the different dialysate fluids. These are similar to previous observations, indicating solute sieving for glucose as a result of free water transport via aquaporins that is not observed with icodextrin.

Table 1. Patient demographics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (Years)</th>
<th>BSA (m²)</th>
<th>Time on PD (Months)</th>
<th>Solute Transport Status (D/P Creatinine at 4 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>2.11</td>
<td>28.2</td>
<td>0.73</td>
</tr>
<tr>
<td>2</td>
<td>61.3</td>
<td>1.73</td>
<td>39</td>
<td>0.801</td>
</tr>
<tr>
<td>3</td>
<td>48.7</td>
<td>2.11</td>
<td>17</td>
<td>0.731</td>
</tr>
<tr>
<td>4</td>
<td>45.67</td>
<td>1.84</td>
<td>17.3</td>
<td>0.651</td>
</tr>
<tr>
<td>5</td>
<td>54.3</td>
<td>2.09</td>
<td>12.5</td>
<td>0.542</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>1.783</td>
<td>23.3</td>
<td>0.75</td>
</tr>
<tr>
<td>7</td>
<td>61.3</td>
<td>1.73</td>
<td>14</td>
<td>0.78</td>
</tr>
<tr>
<td>8</td>
<td>53.3</td>
<td>2.28</td>
<td>18</td>
<td>0.568</td>
</tr>
</tbody>
</table>

*BSA, body surface area; D/P, dialysate/plasma.

Diffusive Transport and Sieving of Solutes and Water

Calculated values for MTAC are shown for both the simplified Garred (Table 2) and Waniewski (Table 3) equations. In each case, MTAC was higher for smaller molecules with a progressive reduction in the absolute values with an increase in solute molecular size. A similar trend was demonstrable with the three different dialysate fluids. This relationship with molecular weight is shown graphically, using the Garred equation (Figure 2). Similar mean values were calculated for the MTAC for HDO with 1.36% glucose dialysate and icodextrin, whereas the diffusion of HDO was significantly greater with hypertonic (3.86%) dialysate. There was also a significantly higher value for the MTAC for urea observed with the 3.86 versus the 1.36% glucose fluid. The use of the Waniewski equation for calculat-
ing the MTAC for HDO and solutes (Table 3) produced similar results to those obtained with the simplified Garred equation.

With the exception of HDO, MTAC observed using icodextrin were consistently and significantly higher that those seen with 1.36 and 3.86% glucose, with the exception of urea in the latter case. Clearly, it was not feasible to calculate the MTAC for glucose with icodextrin, but highly statistical differences were demonstrated for the MTAC of glucose between the two different dialysate glucose concentrations. To visualize more clearly these differences between MTAC obtained in the presence or absence of small solute sieving, we expressed these as ratios (see Table 4). A ratio close to unity would be anticipated if sieving is negligible, and this is seen for water (HDO), when comparing icodextrin with glucose 1.36%, as would be anticipated. The amount of apparent sieving, as indicated by a fall in the ratio, increases with the size of solute and for creatinine and urate is independent of glucose concentration. When comparing glucose 3.86% with icodextrin, this ratio is increased for urea and greater than unity for water. This would be expected for water, which does not sieve by definition, and suggests that the increase in MTAC for urea results in increased transport that overrides the effect of sieving for this solute.

**Discussion**

In this study, we extended our previous measurements of the MTAC of HDO with 1.36% glucose dialysate (14) and showed that this is the same when icodextrin is used. In contrast, the MTAC for other small solutes are different when comparing glucose solutions with icodextrin, most likely reflecting an effect of solute sieving not fully accounted for in the standard equations. The MTAC for HDO, glucose, and, to a lesser extent, urea were increased under conditions of increased convective flow. These observations both conform to the current three-pore model of the peritoneal membrane and yet require its modification if they are to be fully explained.

The experimental design of repeat studies in each individual using all three different dialysate fluids was chosen to minimize potential errors that might result from measured, e.g., residual (sump) volume, and unmeasured differences between individuals, e.g., osmotic hydraulic conductance, peritoneal surface area, and differences in the effect of intraperitoneal hydrostatic pressure. The shape of our ultrafiltration volume profiles for each of the three different dialysate fluids resembled those previously described: Hyperbolic functions for glucose-based dialysate, compared with linear kinetics when using icodextrin (13,22,23). Slight differences were seen compared with one previous study that compared these three solutions in a similar manner in that net intraperitoneal volume started to fall within the 4-h dwell period with 3.86% glucose, and although both studies found sustained ultrafiltration with icodextrin, the net ultrafiltration seen in the present study was less (23). There are some differences between these two studies in terms of their methods and patient characteristics. The use of different intraperitoneal volume markers, 125I-RISA as opposed to dextran 70, seems an unlikely explanation for the apparently lower ultrafiltration volume obtained with icodextrin in this study, as a uniform systematic reduction in ultrafiltration would be anticipated with all three dialysate fluids if this were the case. Furthermore, the net ultrafiltration using glucose in the present study is similar to that obtained in previous studies using this technique, with an isotope recovery within the range of 80 to 90% (19). Alternatively, these observations could reflect true differences in the patient groups studied, in particular differences in the individual peritoneal membrane characteristics such as solute transport (mean D/P creatinine was 0.78 versus 0.69 [23 and our data, respectively]). It is to be expected that individuals with a higher solute transport status, predominantly reflecting a larger small-pore surface area, will achieve better continuous ultrafiltration when using glucose polymers. It should also be remembered that icodextrin is usually used in much longer exchanges, typically 14 h compared with the 4 h used here, when it will achieve larger ultrafiltration volumes. Consistent with previous reports, fluid reabsorption was comparable with all three different dialysate fluids (15,22,23). The well-described phenomenon of sodium sieving was also replicated (Figure 1b), supporting water transport through the transcellular channels under conditions of increased convection when the crystallloid osmotic pressure gradient is at its maximum. This effect is less evident or completely abolished with the use of 1.36% glucose and icodextrin, respectively.

### Table 2. Diffusive transport of water and solutes: MTAC (Garred equation)\(^a\)

<table>
<thead>
<tr>
<th>Dialysate</th>
<th>MTAC (ml/min ± SD)</th>
<th>HDO</th>
<th>Urea</th>
<th>Creatinine</th>
<th>Urate</th>
<th>Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.36% glucose</td>
<td>36.8 (±2.1)</td>
<td>15.3 (±2.63)</td>
<td>8.83 (±2.64)</td>
<td>8.73 (±3.01)</td>
<td>7.4 (±2.39)</td>
<td></td>
</tr>
<tr>
<td>3.86% glucose</td>
<td>49.5 (±6.8)</td>
<td>19.5 (±3.52)</td>
<td>9.2 (±4.2)</td>
<td>10.21 (±4.8)</td>
<td>11.31 (±2.3)</td>
<td></td>
</tr>
<tr>
<td>Icodextrin</td>
<td>39.7 (±7.1)</td>
<td>17.7 (±3.2)</td>
<td>11.6 (±2.7)</td>
<td>11.98 (±2.7)</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

Comparison of dialysate fluids: paired \(t\) test (two-tail)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>(t)</th>
<th>(p)</th>
<th>(t)</th>
<th>(p)</th>
<th>(t)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.36 versus 3.86</td>
<td>0.001</td>
<td>0.01</td>
<td>0.73</td>
<td>0.3</td>
<td>0.0002</td>
<td>—</td>
</tr>
<tr>
<td>1.36 versus icodextrin</td>
<td>0.3</td>
<td>0.06</td>
<td>0.01</td>
<td>0.01</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3.86 versus icodextrin</td>
<td>0.02</td>
<td>0.13</td>
<td>0.02</td>
<td>0.023</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\)MTAC, mass transfer area coefficient.
We recently provided the first measurements for the MTAC for HDO with 1.36% glucose (14). In brief, our findings were that the diffusion of water across the peritoneum relative to other small solutes was in proportion to its diffusion coefficient, which is approximately four times that of glucose, supporting the view that diffusion of water occurs almost exclusively through the small pores. The three-pore model predicts that 95 to 99% of the total pore area is available for diffusion of small solutes; if the aquaporins were available for water diffusion, then the observed value, approximately 40 ml/min, would have been substantially larger, even when allowing for blood flow limitation. This observation is further strengthened by our finding here of an identical MTAC for HDO with 1.36% glucose and icodextrin, as would be predicted by the assumption that HDO cannot itself be sieved.

Our measurements for the MTAC of other small solutes are similar to those previously described for glucose-based dialysate (23–26). In contrast to previous reports (23), we have demonstrated differences in the MTAC for small solutes between glucose-based dialysate and icodextrin and argue that this is best explained by the process of solute sieving not accounted for in the equations. The result is a modest underestimation of the true MTAC when glucose is providing the osmotic driving force. The effect of sieving on the estimate of MTAC was more pronounced as the diffusion coefficient of the solute falls with increasing size (8).

A new and unanticipated finding of this study was the increase in MTAC of HDO and urea under conditions of increased convection. A number of possible explanations for this observation should be considered. First, it is feasible that this simply reflects an artifact as a result of the nature of the mathematical equations used. The simplified Garred and Waniewski formulas both incorporate the initial and subsequent changes in the plasma/dialysate solvent/solute gradient while attempting to account for the convective transport of solute by incorporating the changes in intraperitoneal volume. The latter equation further accounts for convective flow with the use of a correction factor, F. If the increase in MTAC for HDO and urea were due to a “failure” of these equations under conditions of high convection, then it would be anticipated that the same observation would have been made with the other solutes measured, in particular urate and creatinine. In fact, these equations, if anything, tend to overestimate the amount of solute transported by convection. The differences observed in glucose are more difficult to interpret, as with this solute there has also been a substantial change in the initial concentration gradient.

Alternatively, the increase in MTAC for HDO and urea under conditions of increased convection reflect a true increase in small solute diffusion. This increase might reflect (1) recruitment of additional pore area for water by opening a fraction of the aquaporin surface area for diffusion; (2) increased stirring of the interstitium, enhancing mainly the diffusive transport of the smaller molecules, such as water and urea, across the membrane; or (3) an increment in blood flow, as a result of, for example, a vasodilation, mediated either by the hypertonic glucose itself or associated glucose degradation products. The first explanation seems unlikely as the increase in MTAC was similar to those previously described for glucose-based dialysate (23–26). In contrast to previous reports (23), we have demonstrated differences in the MTAC for small solutes between glucose-based dialysate and icodextrin and argue that this is best explained by the process of solute sieving not accounted for in the equations. The result is a modest underestimation of the true MTAC when glucose is providing the osmotic driving force. The effect of sieving on the estimate of MTAC was more pronounced as the diffusion coefficient of the solute falls with increasing size (8).

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Table 4. Comparison of MTAC for water and small solutes obtained using glucose (1.36 or 3.86%) and icodextrin

<table>
<thead>
<tr>
<th>Ratio of MTAC Obtained</th>
<th>HDO</th>
<th>Urea</th>
<th>Creatinine</th>
<th>Urate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio (mean ± SD; 1.36% glucose/icodextrin)</td>
<td>0.95 ± 0.16</td>
<td>0.88 ± 0.14</td>
<td>0.77 ± 0.15</td>
<td>0.73 ± 0.18</td>
</tr>
<tr>
<td>Ratio (mean ± SD; 3.86% glucose/icodextrin)</td>
<td>1.28 ± 0.27</td>
<td>1.11 ± 0.20</td>
<td>0.76 ± 0.25</td>
<td>0.83 ± 0.38</td>
</tr>
</tbody>
</table>

*A ratio below unity is evidence of small solute sieving.

seen with urea as well as HDO, more or less in proportion to their diffusion coefficients, which is twice as fast for water than urea, being 3.4 versus $1.8 \times 10^{-5}$ cm$^2$/s, respectively. Both of the last two explanations would preferentially increase the MTAC for these smaller molecules and require modification of the three-pore model, which in its simplest form treats the peritoneum as an idealized two-dimensional structure without terms for mixing or blood flow.

Previous authors have reported that hypertonic glucose causes a temporary increase in the MTAC for small solutes during the early phase of a hypertonic glucose exchange (27) and suggested that this reflects increased peritoneal blood flow as a result of acute vasodilation (28). We also calculated the MTAC for different solutes at different time points within the dwell (data not shown) and did not find an early increase with any of the solutions used. This difference in observation is likely due to our use of newer, neutral pH, physiologic bicarbonate, "low" glucose degradation product solutions. This would seem to make changes in peritoneal blood flow a less likely explanation of our observation, leaving increased stirring within the interstitium as the probable cause. Previously, it was suggested that mixing could result from the perturbation of unstirred layers of dialysis fluid adjacent to the membrane because vibration of animals during a peritoneal dialysis exchange increased MTAC for all small solutes (29). However, more recent studies of mixing dialysate in cups placed over portions of the peritoneal membrane or even after complete stripping of the mesothelial layer did not affect the MTAC for mannitol (30). Mixing of solutes within the membrane, however, remains a distinct possibility. Because the peritoneal vessels are distributed discretely within the membrane, as envisaged in the distributed model (28,31), there will be considerable regional variability in convective water flow, which, when substantially increased during hypertonic exchanges, will enhance small solute mixing.

In summary, although there are several possible explanations for our findings, each requires consideration of the peritoneal membrane as a three-dimensional structure, for example incorporating the interstitium and the position of blood vessels within it. The relevance of this is clear when the profound changes in peritoneal morphology, in particular interstitial thickening and vascular scarring, observed in the Peritoneal Biopsy Registry are taken into account (32). The relative effects of sieving on water and small solute transport were as predicted by the three-pore model, which might be extended or combined with the distributed model to give a more complete understanding of membrane function.

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