Various aspects of peritoneal water transport

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Chapter 2

A comparison between 1.36% and 3.86% glucose solutions for the assessment of peritoneal membrane function

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Abstract

Objective: To assess peritoneal membrane function with respect to fluid transport, parameters of low molecular weight solute transport, and estimation of the function of peritoneal water channels, comparing the results from a 1.36%/1.5% glucose solution with those from a 3.86%/4.25% glucose solution in standardized peritoneal function tests.

Design: The study was performed in 40 stable continuous ambulatory peritoneal dialysis (CAPD) patients [median age 50 years (range 22-74 years); duration of CAPD 9 months (range:2-45 months)], who underwent two standard peritoneal permeability analyses (SPAs) within one month. One SPA used 1.36% glucose; the other 3.86% glucose. Mass transfer area coefficients (MTACs) and dialysate-to-plasma (D/P) ratios were compared for the two solutions. Also, two different methods of estimating aquaporin-mediated water transport were compared: the sieving of sodium (3.86% glucose) and the difference in net ultrafiltration (ΔNUF), calculated as NUF3.86% SPA - NUF1.36% SPA.

Results: Median NUF in the 1.36% glucose SPA was -46 mL (range: -582 mL to 238 mL); in the 3.86% SPA, it was 554 mL (range: -274 mL to 1126 mL). The median difference in NUF for the two SPAs was 597 mL (range: 90 to 1320 mL). No difference between the two solutions was seen for the MTACs of creatinine (11.4 mL/min for 1.36% vs 12.0 mL/min for 3.86%) and absorption of glucose (64% vs 65%, respectively). Also D/P creatinine was not different: 0.77 (1.36%) and 0.78 (3.86%). However, the ratio of dialysate glucose at 240 minutes and at 0 minutes (D,0/D,240) glucose was 0.34 (1.36%) and 0.24 (3.86%), p<0.01. Values of D/P creatinine from the two glucose solutions were strongly correlated. The intra-individual differences were small and showed a random distribution. Patient transport category was minimally influenced by the tonicity of the dialysate. The minimum D/P Na⁺ (3.86%) was 0.884, and it was reached after 60 minutes. After correction for Na⁺ diffusion, D/P Na⁺ decreased to 0.849 after 120 minutes. The correlation coefficient between the diffusion corrected D/P Na⁺ and ΔNUF was 0.49, p<0.01. An inverse relationship was present between MTAC creatinine and D/P Na⁺ (p< 0.01). This correlation can be explained by the rapid disappearance of the osmotic gradient owing to a large vascular surface area. Such a correlation was not present between MTAC creatinine and ΔNUF.

Conclusions: We conclude that a standardized 4-hour peritoneal permeability test using 3.86%/4.25% glucose is the preferred method to assess peritoneal membrane function, including aquaporin mediated water transport. The D/P Na⁺ after correction for Na⁺ diffusion is probably more useful for the assessment of aquaporin mediated water transport than is ΔNUF obtained with 3.86%/4.25% and 1.36%/1.5% glucose-based dialysis solution.
Introduction

The peritoneal equilibration test (PET), described by Twardowski et al. in 1987, is currently the test most widely used to assess peritoneal transport in continuous ambulatory peritoneal dialysis (CAPD) [1]. The test is performed during a 4 hours dwell with a 2.27%/2.5% glucose dialysis solution. It measures low molecular weight solute transfer and net ultrafiltration. The dialysate/plasma ratio (D/P) of creatinine at the end of the procedure, and the ratio of dialysate glucose at 240 minutes to dialysate glucose at 0 minutes (D<sub>t</sub>/D<sub>0</sub>) are calculated and used as parameters of solute transport. Net ultrafiltration (NUF) is calculated as the difference between the drained volume and the instilled volume. Based on population studies, patients are categorized as low, low-average, high-average or high transporters and recommendations for treatment can be given [2,3].

The standard peritoneal permeability analysis (SPA) is a more sophisticated way to assess peritoneal function [4]. It uses intraperitoneally administered dextran 70 to study fluid kinetics during a 4 hours dwell. The test was originally developed using 1.36%/1.5% glucose. In a SPA, mass transfer area coefficients (MTAC) of low molecular weight solutes are calculated, as are the percentage absorption of glucose and the peritoneal clearances of serum proteins. The PET parameters can be calculated from the SPA data. Conversely the D/P creatinine and the D<sub>t</sub>/D<sub>0</sub> glucose can be used with the drained volume to calculate the MTAC creatinine and the percentage glucose absorption.

It has recently been proposed that a peritoneal function test should be performed with a 3.86%/4.25% glucose dialysis solution. Such a test provides better information on ultrafiltration, because the larger drained volume makes the results less subject to measurement errors, and because the sodium sieving phenomenon associated with a hypertonic glucose solution provides an assessment of aquaporin-mediated water transport [5]. The sodium sieving phenomenon is the result of a decreasing dialysate sodium concentration owing to uncoupled water transport through the peritoneal water channels under influence of the high crystalloid osmotic gradient from the hypertonic solution. The magnitude of the dip in D/P Na<sup>+</sup> is a rough estimate for the function of the water channels [6,7]. Another approach to the assessment of aquaporin mediated water transport is to calculate the difference in net ultrafiltration (ΔNUF) obtained after a 4 hours dwell with 3.86%/4.25% glucose and one with 1.36%/1.5% glucose. In a 1.36%/1.5% glucose dwell the osmotic pressure gradient depends on a small crystalloid osmotic pressure gradient in combination with hydrostatic and colloid osmotic pressures. On the other hand, in a 3.86%/4.25% glucose dwell the crystalloid osmotic pressure is much higher and exceeds the...
other pressure gradients. Consequently, the NUF will depend much more on the number and function of the water channels. Therefore, the ΔNUF, calculated as NUF 3.86%/4.25% - NUF 1.36%/1.5 % will decrease when aquaporin-mediated water transport is impaired.

Given this situation, it follows that a 3.86%/4.25% glucose solution is currently the most informative way to assess peritoneal function. However, normal values for solute transfer in the PET have been obtained with 2.27%/2.5% glucose-based dialysate. Because 3.86%/4.25% glucose initiates more convective transport than 2.27%/2.5% glucose, an effect of dialysis solution osmolality on D/P creatinine and D/D, glucose can not be excluded. In a previous study in 10 CAPD patients, we found that MTACs of low molecular weight solutes were not affected by the tonicity of the solution [8].

The aim of the present study was to compare, in standardized peritoneal permeability analyses in stable CAPD patients, a 1.36%/1.5% glucose dialysis solution (highest diffusion/convection ratio) with a 3.86%/4.25% glucose (lowest diffusion/convection ratio). The parameters of interest were fluid transport, low molecular solute transport, and estimations of the function of peritoneal water channels.

**Patients and Methods**

Two Standard Peritoneal permeability Analyses (SPA) were performed in 40 stable CAPD patients. The test solutions contained 1.36% glucose and 3.86% glucose (both PD1 Dianeal, Baxter B.V., Utrecht, the Netherlands). Table 1 summarizes the composition of the two fluids. The interval between the SPAs was less than one month.

The mean age of the patients was 50 years (range: 22 - 74 years). The mean duration of CAPD therapy was 9 months (range: 2 - 45 months). All patients used commercially available dialysate (Dianeal). None of the patients had peritonitis at the time of the study or during the preceding 4 weeks.

**Procedure**

Each SPA was performed during a 4-hour dwell, as described previously [4]. One test used 1.36%/1.5% glucose, the other used 3.86%/4.25% glucose. In the various patients the SPAs were performed in random order. To avoid the possible effects of the residual volume before the test, and to calculate the residual volume after the test, each SPA was preceded and followed by a rinsing procedure with 1.36%/1.5% glucose. Dialysate samples were taken before instillation and at multiple time points during the test (10, 20, 30, 60, 120, 180 and 240 minutes). Blood samples
were taken at the beginning and at the end of the test-period. A volume-marker, dextran 70 1 g/L (Hyskon, Medisan Pharmaceuticals AB, Uppsala, Sweden), was used to calculate fluid kinetics. To prevent a possible anaphylactic reaction to dextran 70, dextran 1 (Promiten, NPBI, Emmercompascuum, the Netherlands) was injected intravenously before instillation of the test bag [9].

Table 1. Composition of the dialysis solutions used

<table>
<thead>
<tr>
<th></th>
<th>1.36% Glucose (76 mmol/L)</th>
<th>3.86% Glucose (203 mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ (mmol/L)</td>
<td>132</td>
<td>132</td>
</tr>
<tr>
<td>Ca²⁺ (mmol/L)</td>
<td>1.75</td>
<td>1.75</td>
</tr>
<tr>
<td>Mg²⁺ (mmol/L)</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>Cl⁻ (mmol/L)</td>
<td>102</td>
<td>102</td>
</tr>
<tr>
<td>lactate (mmol/L)</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>osmolality (mosmol/L)</td>
<td>347</td>
<td>486</td>
</tr>
<tr>
<td>pH</td>
<td>5.5</td>
<td>5.5</td>
</tr>
</tbody>
</table>

**Measurements**

Total dextran was determined by means of high performance liquid chromatography [10]. Creatinine, urea and urate were measured by enzymatic methods (Boehringer Mannheim, Mannheim, Germany). All electrolytes were determined using ion selective electrodes. Glucose was measured by the glucose oxidase-peroxidase method, using an autoanalyser (SMA-II, Technicon, Terrytown, USA).

**Calculations**

All calculations were performed as previously described by Pannekeet et al [4]. Briefly, changes in intraperitoneal volume are the result of transcapillary ultrafiltration and lymphatic absorption. Both parameters were assessed with the intraperitoneally administered volume marker dextran 70. Transcapillary ultrafiltration (TCUF) was calculated from the dilution of the volume marker, by subtracting the initial intraperitoneal volume (IPV) from the theoretical IPV (when both lymphatic absorption and sampling would not have been present) at any time point. The effective lymphatic absorption rate (ELAR) was calculated as the peritoneal dextran clearance [11].
calculation implies that ELAR includes all pathways of uptake into the lymphatic system, both subdiaphragmatic and interstitial, and will yield higher values than those obtained from the appearance rate of the tracer in the circulation.

The net ultrafiltration is the difference between the transcapillary ultrafiltration and the effective lymphatic absorption. Peritoneal handling of low molecular weight solutes was expressed as MTAC and D/P ratios. The MTAC represents the maximal theoretical diffusive clearance of a solute at $t=0$, before transport has actually started. In this study we used the Waniewski model [12], where the solute concentration was expressed per volume of plasma water [13].

Glucose absorption was calculated as the difference between the amount of glucose instilled and the amount recovered, relative to instilled.

The D/P sodium was calculated as the dialysate sodium concentration divided by the plasma sodium concentration. The difference between initial D/P sodium and the lowest D/P sodium (usually after 1-2 hours) yielded $\Delta$D/P sodium. Correction for Na\(^+\) diffusion from the circulation to the dialysate, known to cause blunting of the decrease in D/P Na\(^+\), was carried out as previously described [14], using the mass transfer area coefficient of urate. The calculated diffused sodium concentration in the dialysate can than be subtracted from the measured concentration at any time point, giving the actual Na\(^+\) sieving.

**Statistical analysis**

Results are presented as medians and ranges, because most data were asymmetrically distributed. Where appropriate means+/-SEM are given. The Wilcoxon’s matched pairs rank sum test was used to compare the results of the two solutions. The Spearman rank correlation analysis was used to investigate possible correlations. Both tests were compared using the method introduced by Bland and Altman [15]. In the Bland-Altman analysis, agreement between two tests is investigated by plotting the differences between pairs of individual values against the means of the same values.

**Results**

**Fluid transport**

Table 2 and Figure 1 give the results of fluid transport kinetics. Median net ultrafiltration was -46 mL for the 1.36%/1.5% glucose exchange and 554 mL when 3.86%/4.25% glucose was used. The median difference between net ultrafiltration for the two dialysis solutions, $\Delta$NUF, was 597 42
mL. Transcapillary ultrafiltration (TCUF) after the 4-hour dwell was 244 mL for 1.36%/1.5% glucose and 803 mL for 3.86%/4.25% glucose. The effective lymphatic absorption rate was not different during the two experiments.

![Figure 1](image-url)

**Figure 1.**

Intraperitoneal fluid changes during the 4 hrs dwell for 1.36%/1.5% glucose (closed circles) and 3.86%/4.25% glucose (open circles).

**Siev ing of sodium**

A marked dip in D/P sodium was found in the initial phase of the 3.86%/4.25% glucose dwell. The dip was even more pronounced after correction for sodium diffusion (Figure 2). The median value for D/P sodium at the beginning of the dwell was 0.927 (0.890 - 1.00). After 60 minutes D/P sodium was significantly lower (0.884, p < 0.001) and after the 240 minutes D/P was still lower than at 0 minutes (0.910), although the difference was no longer significant (p = 0.06).

**Table 2.** Peritoneal fluid kinetics (N=40, median values and ranges) during a 4 hours dwell with 1.36% glucose and 3.86% glucose based dialysate

<table>
<thead>
<tr>
<th></th>
<th>1.36% glucose</th>
<th>3.86% glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net Ultrafiltration (mL/4 hrs)</td>
<td>-46 (-582 to 238)</td>
<td>554* (-274 to 1126)</td>
</tr>
<tr>
<td>Transcapillary Ultrafiltration (mL/4 hrs)</td>
<td>244 (12 to 641)</td>
<td>803* (144 to 1422)</td>
</tr>
<tr>
<td>Effective Lymphatic Absorption Rate (mL/min)</td>
<td>1.3 (0.4 to 3.6)</td>
<td>1.2 (0.2 to 3.5)</td>
</tr>
</tbody>
</table>

* p<0.01 compared to 1.36%/1.5% glucose
When sodium dialysate values were corrected for diffusion, the D/P was 0.859 (p < 0.001) at 1 hour and 0.859 at 4 hours (p < 0.001). The minimum D/P sodium after correction (0.849) occurred at 120 minutes (p<0.001), compared to the initial value.

![Figure 2.](image)

**Dialysate/plasma ratio for sodium during the 4 hrs dwell before correction for sodium diffusion (closed circles) and after correction for sodium diffusion (open circles).**

**Solute transport**

Table 3 summarizes the peritoneal solute kinetics. The MTACs of creatinine, urea and urate were similar for the two test solutions. Also, the D/P creatinine was not different for the glucose 1.36%/1.5% solution as compared with the 3.86%/4.25% (0.78 vs 0.77 respectively). When the values for D/P creatinine from the test solutions were categorized into the various transport groups, only slight changes in category occurred for a few patients, as shown in Table 4.

The median absorption was similar for the two glucose solutions (64% vs 65%). However, the D/Dₜ for glucose was significantly higher for the 1.36%/1.5% glucose solution than for the 3.86%/4.25% solution (0.34 vs. 0.24, p < 0.01).

**Correlations**

A positive, but poor correlation (r=0.29, p=0.068) was present for ΔNUF and ΔD/P sodium, when no correction was made for sodium diffusion. After correction, the correlation coefficient became 0.49 (p=0.001), as shown in Figure 3. A negative correlation between ΔD/P sodium and MTAC creatinine was present: r=-0.34 (p=0.03). After correction for diffusion of sodium from the circulation the r-value increased to -0.57 (p =0.01), as shown in Figure 4.

The D/P creatinine values for 1.36%/1.5% glucose and for 3.86%/4.25% glucose were strongly correlated (correlation coefficient of 0.9, Figure 5). A Bland and Altman plot was used, to investigate the possible presence of systematic errors. It showed a random distribution of the
differences in D/P creatinine between the test solutions (Figure 6).

Table 3. Peritoneal solute kinetics (N=40, medians and range) in a standardized peritoneal permeability analysis with 1.36%/1.5% glucose and 3.86%/4.25% glucose

<table>
<thead>
<tr>
<th></th>
<th>1.36%/1.5% glucose</th>
<th>3.86%/4.25% glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mL/min)</td>
<td></td>
</tr>
<tr>
<td>creatinine</td>
<td>12.0 (6.4-20.1)</td>
<td>11.4 (6.5-21.8)</td>
</tr>
<tr>
<td>Urate</td>
<td>8.9 (4.6-21.0)</td>
<td>8.8 (4.4-22.1)</td>
</tr>
<tr>
<td>Urea</td>
<td>18.0 (10.1-28.6)</td>
<td>19.2 (12.3-28.1)</td>
</tr>
<tr>
<td>D/P creatinine</td>
<td>0.78 (0.53-0.98)</td>
<td>0.77 (0.57-0.94)</td>
</tr>
<tr>
<td>Glucose absorption (%)</td>
<td>64 (34-87)</td>
<td>65 (43-86)</td>
</tr>
<tr>
<td>D240/D0 glucose</td>
<td>0.34 (0.12-0.56)</td>
<td>0.24* (0.09-0.40)</td>
</tr>
</tbody>
</table>

* p <0.01

Figure 3.
Correlation between two different methods for assessing aquaporin-mediated water transport; ∆NUF (horizontal axis) and ∆D/P sodium (vertical axis). The correlation became significant after correction for sodium diffusion from the circulation (lower panel).

Discussion

The aim of the study was to compare the peritoneal permeability characteristics of two glucose solutions with respect to fluid kinetics and solute transport under two glucose solutions, 1.36%/1.5% and 3.86%/4.25%. We wished to assess whether the extra information on aquaporin-mediated water transport, obtained using the dialysis solution with the higher osmolality, would lead to problems interpreting the outcomes of the test usually performed with
Table 4. Comparison of transport categories for both test solutions. Low transport is D/P creatinine exceeding mean - 1SD, low-average is between mean and mean - 1SD, high average is between mean and mean + 1SD and high transport is exceeding mean + 1SD. The bold numbers show corresponding transport groups for both tests.

<table>
<thead>
<tr>
<th></th>
<th>1.36%/1.5%</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Low Average</td>
<td>High Average</td>
<td>High</td>
<td>total</td>
</tr>
<tr>
<td>3.86%/4.25%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Low Average</td>
<td>1</td>
<td>14</td>
<td>2</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>High Average</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>14</td>
<td>15</td>
<td>5</td>
<td>40</td>
</tr>
</tbody>
</table>

1.36%/1.5% glucose (SPA) or 2.27%/2.5% glucose (PET). We chose to compare the solutions with lowest and highest osmolality that are commercially available, assuming that if a 1.36%/1.5% glucose solution (highest diffusion/convection ratio) yielded the same transport parameters as a 3.86%/4.25% solution (lowest diffusion/convection ratio), then the results would not be different for a 2.27%/2.5% glucose solution.

Comparison of 1.36%/1.5% glucose and 3.86%/4.25% glucose
As expected, the 3.86%/4.25% glucose dialysate gave significantly higher transcannular ultrafiltration and net ultrafiltration. The effective lymphatic absorption rate (ELAR), estimated from the disappearance of dextran, was not affected by the osmolality of the test solution. This is consistent with previous publications [8,16,17]. The comparison of MTACs of creatinine, urea and urate revealed no difference between the two dialysis solutions. This result accords with the findings in a previous study from our group in a limited number of patients [8]. The implication is that tonicity has no effect on the effective peritoneal surface area, which is thought to be determined mainly by the number of perfused capillaries, and which can therefore be regarded as an indirect measure of the number of small pores available for transport. The tonicity of the solution had also no effect on the D/P ratio of creatinine. Furthermore, the small intraindividual differences showed a random distribution. Consequently, the transport status of the patients was little influenced. Virga et al. also observed no statistically significant differences between 1.36% and 3.86% glucose using the fast PET [18].
The absorption of glucose was similar in the two tests; however, the D/D₀ glucose ratio for glucose showed a significant difference, with a lower value for the dwell with 3.86%/4.25% glucose. The cause of this inequality is probably the larger drained volume due to the higher transcapillary ultrafiltration for the 3.86%/4.25% glucose dwell, which leads to dilution of the dialysate glucose content.

**Figure 4.**
Correlation between MTAC creatinine (mL/min, horizontal axis) and ΔD/P sodium (vertical axis) before (upper panel) and after (lower panel) correction for sodium diffusion.

**Figure 5.**
Correlation between D/P creatinine for 1.36%/1.5% glucose and 3.86%/4.25% glucose. The correlation coefficient was 0.9 (p<0.01).

Assessment of channel-mediated water transport

In the three pore model, suggested by Rippe et al [19,20], the peritoneum consists of a small number of large pores (transport of macromolecules), a large number of small pores (transport of small solutes) and ultra-small pores (transport of water only). The water channel aquaporin-1 is
likely to be the most important of these peritoneal pores [21,22]. Because the small pores have a very low reflection coefficient to glucose, ultrafiltration through these pores will only be influenced by the tonicity of the dialysis solution to a limited extent. Also, solutions with low hyperosmolality (1.36%/1.5% glucose) will induce little aquaporin-mediated water transport. The ultrafiltration induced by merely hypertonic solutions (3.86%/4.25% glucose) will especially be dependent on channel-mediated water transport. As a consequence, we considered the difference in net ultrafiltration between 1.36%/1.5% glucose and 3.86%/4.25% glucose to be a rough indicator of the number and function of the ultra small pores [23,24].

Another indirect method to estimate the magnitude of transepithelial water transport is to measure the dip in D/P sodium in the initial phase of the dwell. To avoid underestimation of this dip, owing to diffusion of sodium from the circulation to the peritoneal cavity, we corrected for the diffusion. As previously described, the most precise way to perform this correction is probably with the MTAC of urate, but similar values can be obtained with the MTAC of creatinine, which can be calculated from the PET results [14].

In the present study, we investigated these two very different ways - the difference in NUF and dip in D/P sodium - to assess aquaporin-mediated water transport. Although a rather wide range was observed, the two parameters were positively correlated. Our results imply that both methods provide a rough estimate of channel-mediated water transport. For practical purposes, measurement of dialysate sodium concentration at the beginning of a dwell with 3.86%/4.25% glucose and again after 1 hour is probably the easiest way to estimate aquaporin-

Figure 6.
Bland and Altman plot of differences between D/P creatinine for 1.36%/1.5% glucose and 3.86%/4.25% glucose versus their means. No systematic errors were found, implying good agreement between the two tests.
mediated water transport.

The negative correlation between the MTAC creatinine and the $\Delta D/P$ sodium can be explained by the larger peritoneal surface area. The more small pores are available for transport, the higher the absorption of the osmotic agent from the peritoneal cavity to the circulation. As a consequence, aquaporin-mediated water transport will diminish, and net ultrafiltration will be low. No correlation was seen between $\Delta$NUF and the MTAC of creatinine. This also supports the contention that measurement of D/P ratio of sodium after 1 hour during a dwell is probably more reliable as an estimation of transcellular water transport.

We conclude that in the follow-up of peritoneal dialysis patients, a 4 hour PET or SPA test, performed with 3.86%/4.25% glucose is the test of choice. It gives essential extra information on aquaporin-mediated water transport, without losing or blurring information on small solute transport parameters.

References

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