Various aspects of peritoneal water transport

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Chapter 9

Peritoneal transport characteristics with glycerol-based dialysate in peritoneal dialysis

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Abstract

Background: Glycerol is a low-molecular weight solute (MW 92 D), that can be used as an osmotic agent in continuous ambulatory peritoneal dialysis (CAPD). Due to its low molecular weight, the osmotic gradient disappears rapidly. Despite the higher osmolality at the beginning of a dwell, ultrafiltration has been found to be lower for glycerol compared to glucose (MW 180), when equimolar concentrations were used. Previous studies have shown glycerol to be safe for long-term use, but some discrepancies were reported in the transport of small solutes and protein loss.

Objective: To assess permeability characteristics for a 1.4% glycerol dialysis solution compared to 1.36% glucose.

Design: Two standardized peritoneal permeability analyses (SPA), one using 1.4% glycerol and the other using 1.36% glucose, in random order, were performed within a span of 2 weeks in 10 stable CAPD patients. The length of the study dwell was 4 hours. Fluid kinetics and solute transport were calculated and signs of cell damage were compared for the two solutions.

Setting: Peritoneal dialysis unit in the Academic Medical Center in Amsterdam.

Results: Median values for the 1.4% glycerol SPA were as follows: net ultrafiltration 251 mL, which was higher than for 1.36% glucose (12 mL, p<0.01); transcapillary ultrafiltration rate 2.12 mL/min, which was than that for glucose (1.52 mL/min, p=0.01); and effective lymphatic absorption rate 1.01 mL/min, which was not different from the glucose based solution. Calculation of peritoneal reflection coefficients for glycerol and glucose showed lower values for glycerol compared to glucose (0.03 vs. 0.04, calculated with both the convection and the diffusion model). A marked dip in dialysate-to-plasma ratio for sodium was seen in the 1.4% glycerol exchange, suggesting uncoupled water transport through water channels. Mass transfer area coefficients for urea, creatinine and urate were similar for both solutions. Also, clearances of the macromolecules β2-microglobulin, albumin, IgG and α2-macroglobulin were not different for the two osmotic agents. The median absorption was higher for glycerol, 71% compared to 49% for glucose (p<0.01), as could be expected from the lower molecular weight. The use of a 1.4% glycerol solution during a 4-hour dwell caused a small, but significant median rise in plasma glycerol, from 0.22 mmol/L to 0.45 mmol/L (p=0.02). Dialysate cancer antigen 125 (CA-125) and lactate dehydrogenase (LDH) concentrations during the dwell were not different for both solutions.

Conclusions: These findings show that glycerol is an effective osmotic agent that can replace glucose in short dwells and shows no acute mesothelial damage. The higher net ultrafiltration obtained with 1.4% glycerol can be explained by the higher initial net osmotic pressure gradient.
This was seen especially in the first hour of the dwell. Thereafter, the osmotic gradient diminished as a result of absorption. The dip in dialysate-to-plasma ratio for sodium seen in the glycerol dwell can also be explained by this high initial osmotic pressure gradient, implying that the effect of glycerol as osmotic agent is more dependent on intact water channels than is glucose.
**Introduction**

Glucose is the standard osmotic agent for peritoneal dialysis. It is a low molecular weight solute (MW 180 Dalton) that yields high ultrafiltration at relatively low concentrations, is readily metabolized, not immunogenic, cheap and easy to manufacture. One of the disadvantages of glucose as a dialysis solution is its absorption, which averages 66% of the instilled quantity during a four and 75% during a 6 hours exchange [1,2]. This can lead to hyperglycemia, hyperinsulinemia and to obesity, due to the high caloric load [3]. Because of the extensive uptake of intraperitoneally administered glucose, the peritoneal tissues are continuously exposed to extremely high glucose-concentrations, inducing impaired remesothelialization after mesothelial cell damage [4-6]. In addition, high glucose-concentrations lead to non-enzymatic glycosylation of proteins and the formation of advanced glycosylation endproducts (AGEs), as supported by the finding that AGEs are present in the peritoneum of continuous ambulatory peritoneal dialysis (CAPD) patients [7,8]. Another disadvantage of glucose as an osmotic agent is the obligatory acidification of the dialysis fluid before heat-sterilization in order to prevent caramelization.

Because of these unfavorable effects of glucose, other osmotic agents have been investigated. One of them is glycerol, a low molecular weight sugar alcohol of 92 Daltons that is a normal physiological component of plasma. About 70%-90% is taken up by the liver, where it serves as an precursor for gluconeogenesis, and the remainder is metabolized by the kidneys and other tissues [9,10]. Long-term studies performed mainly in Belgium, of stable patients revealed good tolerance, but lower ultrafiltration (UF) rates than expected on the basis of the osmolality of the solutions [11-13]. This is probably explained by the high absorption rates, but in addition, it has been assumed that a lower osmotic reflection coefficient compared to glucose also contributed to this phenomenon. Actual values of these parameters are not available. From previously published studies [14-17] it can be deduced that net UF obtained with the 1.4% glycerol solution is roughly similar to that obtained with 1.36% glucose, despite the markedly higher osmolality of the former (410 mosmol/kg H$_2$O) compared to the latter (347 mosmol/kg H$_2$O). The results of the effect of glycerol-based dialysis solutions and solute transport in these previous studies were equivocal.

The aim of the present study was to compare a 1.4% glycerol dialysis solution with 1.36% glucose in standardized peritoneal permeability analyses, with reference to fluid transport and the transport of low molecular weight solutes and macromolecules in stable CAPD patients. This enabled us to calculate the osmotic reflection coefficient of glycerol. In addition, we studied the possibility of acute toxicity to the mesothelium by investigating the dialysate concentrations of
cancer antigen 125 (CA125) and lactate dehydrogenase (LDH).

**Methods and Patients**

Two Standard Peritoneal permeability Analyses (SPA) were performed in 10 stable CAPD patients. The test solutions consisted of 1.36% glucose (PD1 Dianeal, Baxter B.V., Utrecht, the Netherlands) and a solution containing 1.4% glycerol (Baxter). The composition of the fluids is summarized in Table 1. The protocol was approved by the Committee on Medical Ethics of the Academic Medical Center, Amsterdam, and written informed consent was obtained from all patients after an explanation of the purpose and methods of the study.

Table 1. Composition of the dialysis solutions used

<table>
<thead>
<tr>
<th></th>
<th>1.36% glucose&lt;sup&gt;a&lt;/sup&gt;</th>
<th>1.4% glycerol&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na&lt;sup&gt;+&lt;/sup&gt; (mmol/L)</td>
<td>132</td>
<td>132</td>
</tr>
<tr>
<td>Ca&lt;sup&gt;2+&lt;/sup&gt; (mmol/L)</td>
<td>1.75</td>
<td>1.25</td>
</tr>
<tr>
<td>Mg&lt;sup&gt;2+&lt;/sup&gt; (mmol/L)</td>
<td>0.75</td>
<td>0.25</td>
</tr>
<tr>
<td>Cl (mmol/L)</td>
<td>102</td>
<td>95</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>Osmolality (mOsm/kg H2O)</td>
<td>34&lt;sup&gt;c&lt;/sup&gt;</td>
<td>410</td>
</tr>
<tr>
<td>PH</td>
<td>5.5</td>
<td>6.5</td>
</tr>
</tbody>
</table>

<sup>a</sup>76 mmol/L
<sup>b</sup>152 mmol/L

**Patients**

The patients (9 men and 1 woman) had a mean age of 54 years (range 36 - 76 years) and a median weight of 66 kg (range 63 - 110). The causes for renal replacement therapy were renal vascular disease (in 4 patients), chronic glomerulonephritis (4) and diabetic nephropathy (2). The duration of CAPD therapy ranged from 3 to 50 months, mean 22 months (median 20 months). None of the study patients had urine production of more than 100 mL/24 hours. All patients used commercially available dialysis solution (Dianeal, Baxter). None of the patients had peritonitis at the time of the study or in the preceding 4 weeks.

**Procedure**

The SPAs were performed during 4-hour dwells, as previously described [1]. One test was done with 2 liters of 1.4% glycerol, the other with 1.36% glucose, in random order. They were
preceded and followed by a rinsing procedure with either 1.36% glucose or 1.4% glycerol, depending on the test solution, to avoid the possible effects of the residual volume before the test, and to calculate the residual volume after the test. 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 [18].

Measurements

Total dextran was determined by means of high performance liquid chromatography [19]. Creatinine, urea, urate and LDH were measured by enzymatic methods (Boehringer Mannheim, Mannheim, Germany). All electrolytes were determined using ion selective electrodes. The plasma proteins albumin, IgG and α2-macroglobulin were assessed by nephelometry (BN100, Behring, Marburg, Germany). Beta-2-microglobulin was determined on an IMx system, using a microparticle enzyme immunoassay (MEIA) (Abbott Diagnostics, North Chicago, USA). Glucose was measured by the glucose oxidase-peroxidase method, using an autoanalyzer (SMA-II, Technicon, Terrytown, USA) and glycerol was determined both in dialysate and in plasma by an enzymatic method (Boehringer Mannheim, Mannheim, Germany) [20]. Plasma and dialysate levels of CA125 were assessed by a commercial MEIA, using a monoclonal antibody against CA125 (Abbott Laboratories IMx, IL, USA), validated for measurements in dialysis in our laboratory [21]. Plasma osmolality was measured by depression of freezing point (Advanced Micro Osmometer, Advanced Instruments, Inc., Norwood, MA, USA).

Calculations

All calculations were performed as previously described by Pannekeet et al [1]. Briefly, changes in intraperitoneal volume (IPV) are the result of transcapillary ultrafiltration (TCUF) and lymphatic absorption. Both parameters were assessed with the intraperitoneally administered volume marker dextran 70. The TCUF was calculated from the dilution of the volume marker, by subtracting the initial IPV from the theoretical IPV (when both lymphatic absorption and sampling would not have been present) at any time point. Because TCUF has its maximum value during the initial phase of a dwell, the TCUF rate in the first minute was calculated, using the
Lineweaver-Burke plot, that is, the linear regression between the reciprocal values of the TCUF obtained during the SPA and the reciprocal of time [22]. This also enabled us to calculate the t50, that is, the time it takes to reach 50% of the maximal TCUF. The effective lymphatic absorption rate (ELAR) was calculated as the peritoneal dextran clearance:

$$ELAR (mL/min) = \frac{(Dx_i - Dx_r)}{(Dx_{geom})t}$$

Thus, the ELAR is the difference between the instilled (Dx_i) and recovered (Dx_r) dextran amount, divided by the geometric mean (Dx_{geom}) of the dialysate dextran concentration; t is the duration of the exchange. It is implied that ELAR includes all pathways of uptake into the lymphatic system, both subdiaphragmatic and interstitial. The net UF is the difference between TCUF and the lymphatic absorption. The net UF rate was calculated by dividing the ΔIPV_{240 min} by the dwell time. Peritoneal handling of low molecular weight solutes was expressed as mass transfer area coefficients (MTACs). 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 [23], where the solute concentration was expressed per volume of plasma water [24]:

$$MTAC (mL/min) = \frac{V_m}{t} \cdot \ln \left( \frac{V_{10}^{1-F} (P-D_{10})}{V_t^{1-F} (P-D_t)} \right)$$

where $V_m$ is the mean IPV, $V_{10}$ is the IPV at t=10 minutes, F is a correction factor (0.5) for convective transport, P is the mean plasma concentration of the solute, and $D_{10}$ is the dialysate concentration at t=10 minutes, and $V_t$ and $D_t$ are the V and D parameters at t=240 minutes.

Protein clearances were determined from the amount of protein in the effluent according to:

$$Cl (mL/min) = \frac{Pr_{Dr} + Pr_{RV}}{(Pr_p)t}$$

In this equation, the dialysate protein contents of the drained test bag ($Pr_{Dr}$) and the residual volume ($Pr_{RV}$), are calculated relative to the plasma protein ($Pr_p$) concentration in time. The intrinsic permeability (size-selectivity) of the peritoneal membrane can be represented by the
peritoneal restriction coefficient (RC). The RC is the slope of the linear relationship between the MTACs, or clearances of various solutes, and their free diffusion coefficients in water $D_w$, when plotted on a double logarithmic scale:

$$\text{Clearance} = a \cdot D_w^\sigma$$

in which $a$ is a constant. The RC for macromolecules was assessed as the slope of the regression line between β2-microglobulin, albumin, IgG and α2-macroglobulin and their free diffusion coefficients in water [25].

The reflection coefficient ($\sigma$) for glycerol and glucose across the pores of the peritoneal membrane was calculated using:

$$\sigma = \frac{16}{3} \left( \frac{\alpha_e}{r} \right)^2 - \frac{20}{3} \left( \frac{\alpha_e}{r} \right)^3 + \frac{7}{3} \left( \frac{\alpha_e}{r} \right)^4$$

in which $\alpha_e$ is the solute radius and $r$ the pore radius. To calculate these parameters the solute radii of glucose and glycerol and the small ($\tau_s$) and large ($\tau_l$) pore radii of the peritoneal membrane are needed. The solute radii were determined by calculating their free diffusion coefficients ($D_w$) values, obtained using the principles of Wilke and Chang [26]:

$$D_w = 7.4 \times 10^{-5} \frac{(xMW)^{1/2} T}{\eta V^{0.6}}$$

in which $D_w$ is the free diffusion coefficient, $x$ is the association parameter for water, $MW$ is the molecular weight of the solvent, $T$ is the absolute temperature, $\eta$ is the water viscosity and $V$ is the molecular volume. The values used were: $x$ for water, 2.6; $MW$ for water, 18; $T$ at 20°C, 293; $\eta$, $10^{-3}$ V for glucose, 166.1; and $V$ for glycerol, 96.2. Using the Stokes-Einstein equation $\alpha_e$ can be calculated:

$$\alpha_e = \frac{RT}{6\pi\eta ND_w}$$

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where \( R \) is the gas constant and \( N \) is Avogadro's number. For glucose \( \alpha \) was calculated as 3.12 Å and for glycerol \( \alpha \) was 2.15 Å.

For assessment of the pore radii we used computer simulations as previously described by Rippe and Steli [27]. In this model solute and fluid transport are assumed to occur across the peritoneal membrane by three different pores: a large number of small pores, a small number of large pores, and a set of ultrasmall pores, in which only water transport takes place. This can be described in two different models: In the first, there is a hydrostatic pressure gradient, assumed to be present across the large pores, responsible for the transport of macromolecules by convection (convection model). In the second model the hydrostatic pressure gradient over the large pores was assumed to be approximately 0 mmHg, implying that the transport of macromolecules is only determined by diffusion (diffusion model). In both models, the pore size and the unrestricted area over diffusion distance, that is, the surface area available for diffusion divided by the length of the pathway from the capillary wall to the dialysate, were varied to obtain the best fit between the estimated and measured solute clearances, as described previously by Imholz et al [28]. The average reflection coefficient for both solutes across the peritoneal membrane consists of the sum of the reflection coefficients of each pore set weighted by their respective fractional UF coefficient (\( \alpha_c \) for the transcellular pores, \( \alpha_s \) for the small pores and \( \alpha_l \) for the large pores). For the convection model the values reported by Rippe et al. [27] were used; \( \alpha_c = 0.015 \), \( \alpha_s =0.929 \), and \( \alpha_l = 0.056 \). For the diffusion model we used the values of Imholz et al. [28]; \( \alpha_c = 0.015 \), \( \alpha_s =0.782 \), and \( \alpha_l = 0.203 \).

**Statistical analysis**

Results are presented as median values and ranges, because most data were asymmetrically distributed. Where appropriate, means ± SEM are given. For the comparison of the results of the two solutions, Wilcoxon's matched pairs rank sum test was employed. Spearman rank correlation analysis was used to investigate possible correlations.

**Results**

**Fluid transport**

The results of fluid transport kinetics are given in Table 2 and Figure 1. Median TCUF rate was
higher for the 1.4% glycerol exchange than for the 1.36% glucose exchange, especially during the initial phase of the dwell. The ELAR was not different during both experiments. Consequently, the net UF after 4 hours was higher with glycerol (251 mL vs. 12 mL).

Table 2. Peritoneal fluid kinetics (N=10, median values and ranges) during a 4 hour dwell using 1.36% glucose and 1.4% glycerol-based dialysate

<table>
<thead>
<tr>
<th>Net ultrafiltration (mL)</th>
<th>1.36% glucose</th>
<th>1.4% glycerol</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCUF rate (mL/min)</td>
<td>1.52 (0.94-2.12)</td>
<td>2.12 (1.57-3.75)</td>
<td>0.01</td>
</tr>
<tr>
<td>TCUF rate 0-1 min (mL/min)</td>
<td>7.24 (2.45-10.0)</td>
<td>11.52 (4.7-15.1)</td>
<td>0.024</td>
</tr>
<tr>
<td>T50 (min)</td>
<td>41.5 (27.4-71.4)</td>
<td>36.9 (24.5-63.2)</td>
<td>0.675</td>
</tr>
<tr>
<td>Effective lymphatic absorption rate (mL/min)</td>
<td>1.18 (0.59-2.22)</td>
<td>1.01 (0.73-3.11)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

TCUF rate = transcapillary ultrafiltration rate

Sieving of sodium

A marked dip in dialysate-to-plasma ratio (D/P) of sodium was found during the first hour of the glycerol dwell (Figure 2). The median value for D/P sodium at the beginning of the dwell was 0.925 for glucose and 0.956 for glycerol (not significant). After 60 minutes, D/P glycerol was significantly lower (0.904) than that of glucose (0.921, p=0.036).

Figure 1.
The time course of transcapillary UF (closed circles), effective lymphatic absorption (closed squares) and the resulting change in intraperitoneal volume (closed triangles) with 1.36% glucose (left panel) and 1.4% glycerol (right panel), are compared. * p<0.05 compared to 1.36% glucose.
Table 3. Peritoneal membrane characteristics (median and ranges) after fitting the measured solute clearances with model I (convection through large pores only) and model II (diffusion through large pores only). Median values and ranges are given.

<table>
<thead>
<tr>
<th></th>
<th>Model I</th>
<th>Model II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.36% glucose</td>
<td>1.4% glycerol</td>
</tr>
<tr>
<td>Small pore radius (Å)</td>
<td>47.5 (43-53.6)</td>
<td>43.2 (34.7-50.0)*</td>
</tr>
<tr>
<td>Large pore radius (Å)</td>
<td>142.6 (121.9-172.2)</td>
<td>145.2 (120.5-169.2)</td>
</tr>
<tr>
<td>Δs/Δx (m)</td>
<td>138.55 (88.0-175)</td>
<td>132.2 (91.0-170.0)</td>
</tr>
<tr>
<td>Δl/Δx (m)</td>
<td>33.8 (20.0-78.0)</td>
<td>32.7 (19.6-45.7)</td>
</tr>
</tbody>
</table>

Δs/Δx and Δl/Δx are the unrestricted pore areas over unit diffusion distance for the small and large pores.

* p=0.03, compared to 1.36% glucose

**Figure 2.**
Dialysate-to-plasma ratios of sodium (D/P sodium) during 4-hour dwells using 1.36% glucose (open circles) and 1.4% glycerol (closed circles) are compared. During the dwell with glycerol, a decrease in D/P Sodium was observed, indicating sieving of sodium through the ultra small pores. Data are expressed as medians for 10 stable CAPD patients.

*Reflection coefficient*

The pore sizes in the convection model and the diffusion model obtained with computer simulations are given in Table 3. The reflection coefficient of glycerol averaged 0.03 and that of glucose 0.04 in both models, as shown in Table 4.

**Figure 3.**
Plasma concentrations of glycerol before and after a 4-hour dwell using 1.4% glycerol dialysate are given for each patient. Higher values were measured after the glycerol dwell; this difference was statistically significant, p<0.05.
Solute transport

The peritoneal solute kinetics are summarized in Table 5. The MTACs of urea, creatinine and urate and clearances of β2-microglobulin, albumin, IgG and α2-macroglobulin were similar for both test solutions. The restriction coefficient to macromolecules was also not different.

The median absorption was higher for glycerol (71%) than for glucose (49%), as could be expected from the lower molecular weight of glycerol. The use of a 1.4% glycerol dialysis solution caused a small, but significant rise in plasma glycerol from 0.22 mmol/L to 0.45 mmol/L, p=0.02 (Figure 3).

Table 4. The reflection coefficients (× 10⁻²) of the dialysis solutions, 1.36% glucose and 1.4% glycerol, calculated when using the convection model and using the diffusion model. For each model the mean reflection coefficient across the peritoneal membrane (σ) and the fractional reflection coefficients over the small and large pores (σs and σl) are given.

<table>
<thead>
<tr>
<th></th>
<th>1.36% Glucose</th>
<th>1.4% Glycerol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convection model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>σ</td>
<td>3.51</td>
<td>2.71*</td>
</tr>
<tr>
<td>σs</td>
<td>2.14</td>
<td>1.29*</td>
</tr>
<tr>
<td>σl</td>
<td>0.26</td>
<td>0.16*</td>
</tr>
<tr>
<td>Diffusion model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>σ</td>
<td>3.74</td>
<td>2.74*</td>
</tr>
<tr>
<td>σs</td>
<td>2.86</td>
<td>1.58*</td>
</tr>
<tr>
<td>σl</td>
<td>0.05</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

*p < 0.0001 compared to 1.36% glucose

Markers of toxicity

The concentrations of CA125 and LDH during the dwell did not show an abrupt rise during the instillation of either test solution, indicating there was no direct cytotoxicity to the mesothelium (Figure 4). The gradual rise in CA125 and LDH that was observed during the four hours observation period suggests a continuous release from mesothelial cells for CA125 and a combination of release and transperitoneal transport for LDH.

Discussion

The results of the present study show that 1.4% glycerol is an effective osmotic agent, with greater net UF than 1.36% glucose. No effect on MTACs of low molecular weight solutes was found, nor was there any effect on the clearances of macromolecules. Previous studies on this
Table 5. Peritoneal solute kinetics (N=10, medians and range) in a standardized peritoneal permeability analysis using 1.36% glucose and 1.4% glycerol

<table>
<thead>
<tr>
<th></th>
<th>1.36% Glucose</th>
<th>1.4% Glycerol</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTAC (mL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>18.4 (13.3-21.4)</td>
<td>18.2 (14.0-23.3)</td>
<td>1</td>
</tr>
<tr>
<td>Creatinine</td>
<td>10.3 (5.9-12.4)</td>
<td>9.2 (5.4-12.1)</td>
<td>0.36</td>
</tr>
<tr>
<td>Urate</td>
<td>7.3 (4.4-9.7)</td>
<td>6.9 (4.5-9.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>Clearance (µL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β2-microglobulin</td>
<td>911 (583-1389)</td>
<td>995 (586-1598)</td>
<td>0.8</td>
</tr>
<tr>
<td>Albumin</td>
<td>113 (62-590)</td>
<td>104 (70-186)</td>
<td>0.61</td>
</tr>
<tr>
<td>IgG</td>
<td>53 (22-130)</td>
<td>60 (37-94)</td>
<td>0.41</td>
</tr>
<tr>
<td>α2-macroglobulin</td>
<td>17 (7-32)</td>
<td>23 (7-37)</td>
<td>0.31</td>
</tr>
<tr>
<td>Restriction coefficient</td>
<td>2.35 (1.99-2.69)</td>
<td>2.23 (1.91-2.65)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

subject are equivocal. The results of these studies are summarized in Table 6. Most studies on the use of glycerol in peritoneal dialysis focussed mainly on UF, side effects and its effects on plasma glycerol levels [9-12,29,30]. Only a few studies have been published about peritoneal permeability characteristics and fluid kinetics [14-17]. All these acute studies showed good tolerance and no clinically evident side effects.

Table 6. Summary of the published studies on peritoneal transport of small solutes, fluid and macromolecules using glycerol-based versus glucose-based peritoneal dialysis solutions

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pts</th>
<th>Dwell time (no)</th>
<th>Concentration glucose/glycerol (%)</th>
<th>UF transport small solutes (mL)</th>
<th>Transport of plasma proteins</th>
<th>Transport of small solutes</th>
<th>Absorption (glucose/glycerol (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heaton [14]</td>
<td>6</td>
<td>6</td>
<td>1.36/0.85</td>
<td>85/67</td>
<td>↓</td>
<td>NR</td>
<td>71/86</td>
</tr>
<tr>
<td>De Paepe [15]</td>
<td>6</td>
<td>4</td>
<td>1.36/0.85</td>
<td>258/44</td>
<td>=</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lindholm [16]</td>
<td>4</td>
<td>6</td>
<td>1.36/0.85</td>
<td>499/216</td>
<td>=</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Waniewski [17]</td>
<td>4</td>
<td>6</td>
<td>3.86/2.5</td>
<td>808/369</td>
<td>=</td>
<td>↑</td>
<td>74/93</td>
</tr>
</tbody>
</table>

NR=not reported; NS= not significant

Fluid kinetics

All published experiments in patients have been performed with fluids delivered by Travenol/Baxter. In these studies 0.85% glycerol (92 mmol/L) was compared to 1.36% glucose (76 mmol/L), 1.4% glycerol (152 mmol/L) to 2.27% glucose (126 mmol/L) and 2.5% glycerol (272 mmol/L) to 3.86% glucose (214 mmol/L). These studies showed that the glycerol-based
solutions induced less net UF during 4- to 6- hour exchanges than their glucose-based counterparts, despite the higher initial osmolality of the glycerol solutions. Similar observations were made in experiments in rats [31]. Although higher absorption rates of glycerol compared to glucose were found [14,16], the difference between the osmotic agents seemed too small to fully explain the low UF with glycerol. Therefore, a smaller peritoneal reflection coefficient for glycerol than for glucose has been postulated. However, inspection of the intraperitoneal fluid profiles described in literature [14,16] shows a similar increase during the first hour of an exchange, thereafter the intraperitoneal volume was smaller during the glycerol dwells. As a result, net UF after 4- to 6-hour exchanges obtained with 1.36\% glucose was in the same order of magnitude as net UF obtained with 1.4\% glycerol [15,16]. As we wanted similar UF profiles to calculate the reflection coefficient, we chose to compare 1.4\% glycerol with 1.36\% glucose, despite the difference in osmolality of the two solutions. The fluid profiles showed a steeper initial rise in IPV for glycerol than for glucose. When calculating the TCUF rate in the first minute of the dwell, a significantly higher value for glycerol was found. Also, the TCUF rate was significantly higher in the initial phase of the dwell compared to the whole dwell, for both solutions. Kinetic modeling using the pore model, suggested by Rippe and Stelin, showed similar values for the small and large pore radii, and for the unrestricted pore areas over unit diffusion distance, irrespective of whether they were calculated on the glucose experiments or on the glycerol experiments. These parameters were also similar to previously published values for 1.36\% glucose [32]. However, the reflection coefficient for glycerol was significantly lower than that for glucose with a mean difference of 0.01 between the two osmotic agents. Using these values, it can be calculated that the initial osmotic pressure gradient averaged 28 mmHg for glucose and 55 mmHg for glycerol. This may explain the steeper rise in intraperitoneal volume obtained with 1.4\% glycerol.

Aquaporin-1 is the water channel in peritoneal endothelial cells [33]. It is not permeable to small solutes such as glucose, urea and glycerol [34]. Therefore, the reflection coefficient of glucose and glycerol to this water channel is 1.0. This explains the very marked sieving of sodium observed during the first hour of the glycerol exchanges. As the sieving of sodium is likely to be caused by channel-mediated water transport, our findings imply that the overall osmotic effect of 1.4\% glycerol is more dependent on the integrity of peritoneal aquaporins than that of 1.36\% glucose. Lymphatic absorption was similar for the two solutions, implying that glycerol has no influence on this parameter.
Solute kinetics

In the previous studies on this subject, equilibration patterns between dialysate and plasma levels of urea, creatinine and potassium were similar for glucose and glycerol solutions - De Paepe et al [15], Lindholm et al [16] and Waniewski et al [17] - although Heaton et al.[14] found decreased equilibration rates for small solutes. In our study, the use of glycerol revealed no difference in peritoneal handling of low-molecular weight solutes, suggesting that glycerol has no influence on the vascular peritoneal surface area.

A point of concern with using glycerol exclusively as the dialysis solution is the high absorption of glycerol, leading to accumulation of glycerol in the plasma. This can give rise to a hyperosmolar syndrome in which glycerol sometimes needs to be discontinued because of thirst and the inability to remain on dry weight [10,15]. It can also interfere with the measurement of blood-triglycerides, which have to be corrected for free glycerol concentrations [9,13,15]. In this single short-term administration, we found indeed a small but significant rise in plasma glycerol. Plasma osmolality, however, remained stable. The effect on plasma osmolality when using more exchanges per day has to be examined.

In the earlier studies, clearances of macromolecules were either not assessed [14,15] or were reported to be increased when glycerol was used [16]. Lindholm’s group found, in 12 paired observations in 4 patients, that loss of total protein was greater on glycerol than on glucose. After more complex kinetic modeling this difference was no longer significant, probably because of the small number of patients [17]. In our study no higher clearance of any of the serum proteins was found on glycerol compared to glucose.

The transport of macromolecules is dependent on both the vascular peritoneal surface area and the intrinsic permeability of the peritoneal membrane, represented by the restriction coefficient [25,35]. Since changes in intrinsic permeability to macromolecules probably reflect change in large pore size, the present study showed no indication that glycerol has any effect on this parameter.

Markers of toxicity

We found no direct toxicity of either dialysis solution. Previous studies suggested that glycerol was less toxic than glucose [36]. The pH of glycerol containing dialysate is higher (6.5) compared to glucose (5.5), which is likely to increase biocompatibility and is probably responsible for the reduction in abdominal pain during instillation [9]. Breborowicz et al. found cytotoxicity of various hyperosmolar osmotic agents in in vitro experiments when mesothelial cells were incubated for 24 hours with glucose, glycine, glycerol and mannitol for 24 hours [4]. A rise in
LDH concentration in the culture medium was measured as marker of cell lysis. Cell-growth was inhibited most and LDH was highest with the use of glucose in high concentrations (90 mM), and the least growth retardation and cell lysis were found when glycerol was used.

![Figure 4.](image)

Effluent concentrations of CA125 (left panel) and LDH (right panel) during the 4-hour dwell for 1.36% glucose (open circles) and 1.4% glycerol (closed circles) are plotted. No significant differences were seen. The gradual rise in dialysate concentration of both markers was probably due to continuous release from cells or peritoneal transport.

Dialysate concentrations of CA125 can serve as a marker of mesothelial cell mass [21,37]. An abrupt rise in CA125 concentration after instillation of the dialysis solution would suggest direct mesothelial injury. Data from our laboratory in 4-hour dwells with 1.36% and 3.86% glucose and 7.5% Icodextrin showed only a gradual rise in dialysate LDH and CA125 levels, suggesting no acute cell lysis had occurred [38]. In the present experiments, the CA125 concentration as well as the dialysate LDH concentration, also showed a gradual rise. Therefore the observed increase is most likely the result of a continuous release from cells or peritoneal transport [39].

It can be concluded that 1.4% glycerol is an effective osmotic agent with higher TCUF compared to 1.36% glucose during short exchanges. The higher TCUF rate for glycerol is due mainly to the higher osmolality of the solution, which exceeds the negative effects of the lower reflection coefficient. Therefore, the osmotic pressure gradient at the beginning of a dwell is higher with
glycerol. Consequently, the TCUF rate was highest at the beginning of a dwell and diminished later on because of the high absorption of glycerol, a consequence of the lower molecular weight. This high initial osmotic pressure gradient gave a marked dip in D/P sodium, a result of transcellular water transport. We therefore suggest that the effect of glycerol as osmotic agent is more dependent on intact aquaporin-mediated water transport than that of glucose.

References


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